IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

PFIZER INC., PHARMACIA CORP., PHARMACIA & UPJOHN INC., PHARMACIA & UPJOHN COMPANY, G.D. SEARLE & CO., G.D. SEARLE LLC, SEARLE LLC (DELAWARE) and SEARLE LLC (NEVADA) Plaintiffs, v. TEVA PHARMACEUTICALS USA, INC. Defendant.	))))))))))))))))	**CONFIDENTIAL - OUTSIDE ATTORNEYS' EYES ONLY** Civil Action No: 04-754 (JCL)

<u>EXPERT REPORT OF DR. WILLIAM L. JORGENSEN</u>

I submit this report pursuant to Fed. R. Civ. P. 26 to set forth the opinions I have formed and may offer at trial of this action.

I. BACKGROUND

Education and Experience

1. I am currently the Whitehead Professor of Chemistry at Yale University.

2. I received an A.B. in Chemistry in 1970 from Princeton University, and was awarded a Ph.D. in Chemical Physics from Harvard University in 1975, during which time I worked under the direction of Nobel Laureate E. J. Corey.

3. From 1975-1990, I was employed by Purdue University's Department of Chemistry. I began my teaching career at Purdue in 1975 as an Assistant Professor, and in 1979 I was promoted to the position of Associate Professor. I was again promoted in 1982, to Professor of Chemistry, a position I held until 1990. While at Purdue, I also served as the Head of the Organic Chemistry Division from 1984-1987, and was the Herbert C. Brown Professor of

Chemistry from 1985-1990. In 1989 I taught at Harvard University as a Visiting Professor, and in 1990 I accepted the position at Yale University that I hold today.

4. I have studied pharmaceutical chemistry throughout my career. My research has concentrated on structure activity relationships (SAR) for numerous classes of drugs including COX-2 inhibitors. I also have experience synthesizing compounds and searching for new drugs. I have published more than 300 articles in refereed journals and numerous meeting abstracts on topics in organic and computational chemistry, many concerning the properties and reactivity of organic compounds, and drug design and discovery. My publications include papers dealing with SAR issues and selectivity of COX-2 inhibitors based on varying structures.

5. I have consulted regarding computational chemistry and drug design, often concerning problems with biological activity and pharmacological properties, for many pharmaceutical companies, including Pharmacia, Agouron, Parke Davis, Pfizer, Amgen and Johnson & Johnson. I have served on the Scientific Advisory Boards of five pharmaceutical companies.

6. I have developed software for the design of drugs. A key example is the program QikProp, which provides predictions of the chemical and physical properties of organic molecules, including drugs. It takes as input a structure of a molecule and it outputs predictions for properties including aqueous solubility, octanol/water partition coefficient (log P_{ow}), cell permeability, brain/blood partition coefficients, primary metabolites, etc. The software is licensed by more than 150 pharmaceutical and biotech companies.

7. I have presented over 500 invited lectures during my career. I was also a member of the NIH Medicinal Chemistry Study Section from 2001-2004, and I have consistently

received research support from institutions including the National Science Foundation and the National Institute of Health.

8. A copy of my Curriculum Vitae, including a list of my publications, is attached as Exhibit A.

Compensation

9. I am being compensated for my time as an expert witness at the rate of $250 per hour plus reasonable expenses. My compensation is unaffected by the outcome of this litigation.

Prior Testimony

10. In the past four years, I have testified as an expert in the following proceedings:

a. G.D. Searle & Co. v. Unipharm Ltd., Patent Application No. 136532 (Israel).

II. MATERIALS CONSIDERED

11. In forming my opinions and preparing this report, I have reviewed and relied upon the materials cited and listed in Exhibit B, attached to this report, and my many years of experience in pharmaceutical chemistry. This work is reflected in my publication list.

III. SUBJECT MATTER ABOUT WHICH I EXPECT TO TESTIFY

12. I presently plan to give opinions and testify concerning:

a. the history of NSAIDs and the search for a safer NSAIDs;

b. a tutorial on medicinal chemistry;

c. the disclosure of the patents-in-suit, the Merck ’196 application and the Fujisawa references;

d. one of ordinary skill in the art would not expect the genus of compounds disclosed in the Merck ’196 application to be COX-2 selective or anti-inflammatory;

e. the Teva Pharmacophore – the lack of support in the Merck ’196 application and the lack of an expectation that the compounds within the Teva Pharmacophore would be COX-2 selective;

f. the lack of a motivation to synthesize heterocycles not disclosed by the Merck ’196 application;

g. there is no basis for Teva’s “twelve obvious compounds”;

h. the Fujisawa references are more relevant than the Merck ’196 application and other references cited by Teva;

i. celecoxib is closer in structure to SC-58125 than to example 29-3 of the ’829 Fujisawa reference;

j. rofecoxib (Vioxx®) is as close to celecoxib (Celebrex®) as any other compound within the Teva Pharmacophore; and

k. meloxicam’s structure is distinct from, and does not teach, celecoxib.

13. I may address other matters in response to reports or other evidence offered by Teva. I reserve the right to supplement or amend my opinions in response to opinions expressed by defendant’s experts, or in light of any additional evidence, testimony, discovery or other information relating to the aforementioned issues that may be provided to me after the date of this report. I further reserve the right to rely on any documents used by Teva’s experts. In addition, I expect that I may be asked to consider and testify about issues that may be raised by defendant’s experts in their reports or at trial. In connection with my testimony, I may rely upon certain graphic or demonstrative exhibits that have not yet been prepared.

IV. NSAIDS AND NSAID RESEARCH EFFORTS

14. NSAIDs have been known for more than 100 years, since the discovery of aspirin. NSAIDs have been used to treat arthritis and other inflammation related conditions, and have become one of the most widely used classes of drugs in the world.[1] Despite their widespread acceptance and use, the mechanism of action of NSAIDs was largely unknown until 1971, when Sir John Vane reported that NSAIDs act by inhibiting prostaglandin synthesis.[2] NSAIDs work by inhibiting the cyclooxygenase (COX) enzyme, which is the enzyme involved in the first step of prostaglandin synthesis. Prostaglandins, however, are not involved solely in inflammation. They are also involved in certain "housekeeping" functions, such as maintaining the mucosal lining in the stomach and platelet aggregation. Since NSAIDs inhibit production of prostaglandins responsible for these housekeeping functions, the use of NSAIDs often results in undesirable side effects including gastrointestinal complications such as ulcers, internal bleeding and, in some cases, death.[3]

15. As a result of these undesirable side effects, pharmaceutical companies spent considerable efforts over the decades to develop NSAIDs that had a superior safety profile. In the early 1990's a second cyclooxygenase enzyme, encoded by a second COX gene, was identified. This second enzyme (COX-2 or the "inducible cyclooxygenase enzyme") is responsible for the production of prostaglandins associated with inflammation, while a separate

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1 *See, e.g.*, Lehmann & Beglinger, "Impact of COX-2 Inhibitors in Common Clinical Practice a Gastroenterologist's Perspective," *Current Topics in Medicinal Chemistry*, 2005, vol. 5, pp. 449-464, 449. (PFC01591975-90).

2 *See, e.g.*, Lombardino, "Nonsteroidal Antiinflammatory Drugs," 1985, pp. 114-115 (PFC01548171-319).

3 *See, e.g.*, Robitaille, "Improved Nonsteroidal Anti-inflammatories," *The Canadian Journal of CME*, July 1998, pp. 85-95, 86. (PFC01578962-72).

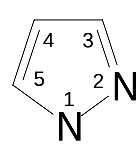
cyclooxygenase enzyme (COX-1 or the "constitutive cyclooxygenase enzyme") is associated with the prostaglandins involved in housekeeping functions such as maintaining the mucosal lining. By the mid-1990's, many researchers believed that an NSAID that could inhibit the COX-2 enzyme and not inhibit the COX-1 enzyme had the potential to provide anti-inflammatory activity without the undesirable side effects.[4]

V. LEVEL OF ORDINARY SKILL IN THE ART

16. A person of ordinary skill in the art to whom the patents-in-suit are directed would be a medicinal chemist, who has likely received a B.S. or higher degree with a focus on organic or pharmaceutical chemistry. The person of ordinary skill in the art would also likely have several years of experience in the pharmaceutical industry. This experience would also likely allow the person to become more knowledgeable about biological assays, animal testing, and pharmacological issues including biolavailability and metabolism.

VI. BACKGROUND OF MEDICINAL CHEMISTRY

17. A heterocycle is a ring structure made up of carbon atoms and one or more of the following non-carbon atoms: sulfur, nitrogen, and oxygen. The non-carbon atoms are commonly referred to as the heteroatoms. For ease of reference, the positions of a heterocycle are often numbered as shown below (with respect to a pyrazole). Positions on the heterocycle are commonly referred to by their numbered positions, *i.e.*, 1-position, 2-position, etc.



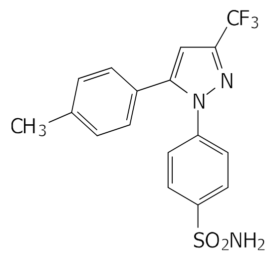
18. The structure of a chemical compound can be referred to by

4 *See, e.g.*, Donnelley & Hawkey, "Review Article: Cox-II inhibitors–a new generation of safer NSAIDs?", *Aliment Pharmacol Ther*, 1997, vol. 11, pp. 227-236, 229 (PFC01602819-28).

words or a structural drawing with letters representing the components. For example, the chemical structure of celecoxib can be referred to as follows:

a. 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl] benzenesulfonamide; or

b.



19. Chemical structures are routinely drawn as two-dimensional representations for convenience. Chemical structures are, however, three-dimensional. Thus, although the two-dimensional drawings of two chemical structures may look similar to the untrained eye, the actual three-dimensional structures of the molecules could be very different.

20. Drugs often work by binding to a particular molecular site, commonly referred to as the active site of the target, such as, an enzyme. The active site of an enzyme has a specific shape and only allows compounds of a complementary shape to bind, analogous to a lock and key.[5] Thus, even the slightest change to the three-dimensional chemical structure of a compound can result in a significant effect on its ability to bind to the active site. In 1993, neither the structures of the COX-1 and COX-2 enzymes, nor the structures of the active sites to which inhibitors of COX-1 and COX-2 would bind, were known.[6]

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5 *See, e.g.* Korolkovas, "Essentials of Molecular Pharmacology," John Wiley & Sons, 1970, pp. 8-11, 41 (PFC01603261-67).

6 Picot, "The X-ray crystal structure of the membrane protein prostaglandin HS synthase-1," *Nature*, 1994, 367: 243-249 (COX-1) (PFC001198834-40); Kurumbail, "Structural basis for selective inhibition of cyclooxygenase-2 by anti-inflammatory agents," *Nature*, 1996, 384: 644-648 (COX-2) (PFC00238777-81).

21. It is well known that small changes in chemical structure can lead to vast differences in a compound's chemical and pharmacological properties.[7] For example, water contains two hydrogen atoms and one oxygen atom (H_2O). As one is well aware, water is non-toxic and makes up much of the body. Simply adding a single oxygen atom to a water molecule will form hydrogen peroxide (H_2O_2), which is toxic if consumed.

22. The process of determining the effects that small structural changes have on the activity of a molecule is referred to as the study of structure-activity relationships ("SAR"). In order to develop SAR on a single series of compounds built around a core structure such as a particular heterocycle, pharmaceutical companies routinely synthesize and analyze hundreds of compounds. As data is being generated, one looks at the data to determine if conclusions can be reached regarding the effect(s) that certain changes have on the activities and properties of the compounds. These conclusions then influence the decision on what compounds to try to make and test next. Conclusions based on SAR data are often subjective and will depend on the interpretation of the scientist reviewing the data. There is also normal statistical uncertainty in any measured quantities, and the assays yielding the SAR data are generally complicated, involving measuring responses of an *in vitro* or *in vivo* biological system. Thus, two scientists looking at a limited amount if data can come to different conclusions because of the complexity and unpredictability inherent in medicinal chemistry.

23. A priori activity predictions are generally not possible because even the slightest changes to a molecule often produce significant differences in activity. Thus, even after

[7] *See, e.g.,* Korolkovas, "Essentials of Molecular Pharmacology," John Wiley & Sons, 1970, pp. 8-11, 41 (PFC01603261-67); Song et al., "Synthesis, Structure-Activity Relationships, and In Vivo Evaluations of Substituted Di-*tert*-butylphenols as a Novel Class or Potent, Selective, and Orally Active Cyclooxygenase-2 Inhibitors. 2. 1,3,4- and ,2,4-Thiadiazole Series" *J. Med. Chem.*, 1999, 42:1161-1169, Table 1; Lombardino, "Nonsteroidal Antiinflammatory Drugs," 1985, pp. 114-115 (PFC01606510-653).

developing SAR conclusions, one does not know with any certainty what effect making a specific change will have on the activity of a molecule without making and testing it.

24. It should also be noted that there is a strong bias in reporting SAR data in the literature, particularly in patents, toward reporting successes rather than failures.

VII. THE PATENTS-IN-SUIT

25. The patents-in-suit are directed to a genus of compounds that have anti-inflammatory properties and less harmful side effects.[8]

26. U.S. 5,466,823 (the "'823 patent"), entitled "Substituted Pyrazolyl Benzenesulfonamides," is directed to a genus of compounds that are taught to be useful "for treating inflammation and inflammation-related disorders."[9] The genus of claim 1 of the '823 patent, which includes celecoxib, is:

a. the heterocycle must be a pyrazole;

b. the substituent attached to the nitrogen at the 1-position of the pyrazole must be a phenyl ring which is substituted at the 4-position of the phenyl ring (R_1) with a sulfamyl substituent;

c. the substituent at the 3-position of the pyrazole (R_2) is a haloalkyl;

d. the substituent at the 4-position of the pyrazole (R_3) is a hydrogen or alkyl; and

e. the substituent at the 5-position of the pyrazole (R_4) is a aryl, cycloalkyl, and cycloalkenyl and can be optionally substituted with one or more of the following: halo, alkylthio, alkylsulfinyl, alkyl, alkylsulfonyl, cyano, carboxyl, alkoxycarbonyl, amido, N-monoalkylamido, N-monoarylamido, N,N-dialkylamido, N-alkyl-N-arylamido, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl, haloalkoxy, sulfamyl, N-alkylsulfamyl, amino, N-alkylamino, N,N-dialkylamino, heterocyclic, nitro and acylamino.

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8 *See, e.g.,* '823 patent, col. 3, lns. 23-26 (DX-012).

9 '823 patent, col. 1, ln. 5-10 (DX-012).

27. Claim 9 of the ’823 patent specifically claims celecoxib. The ’823 patent includes 30 numbered examples and *in vivo* biological data from a rat carrageenan foot pad edema test for three compounds.

28. U.S. 5,563,165 (the “’165 patent”), is entitled “Substituted Pyrazolyl Benzenesulfonamides For the Treatment of Inflammation,” and is directed to the pharmaceutical compositions of a genus of compounds which are taught to be useful “for treating inflammation and inflammation-associated disorders.”[10] The genus of compounds in claim 1 is:

a. the heterocycle must be a pyrazole;

b. the substituent attached to the nitrogen at the 1-position of the pyrazole must be a phenyl ring which is substituted at the 4-position of the phenyl ring (R_1) with a sulfamyl, halo, alkyl, alkoxy, hydroxyl and haloalkyl;

c. the substituent attached at the 3-position of the pyrazole (R_2) is hydrido, halo, haloalkyl, cyano, nitro, formyl, carboxyl, alkoxycarbonyl, carboxyalkyl, alkoxycarbonylalkyl, amidino, cyanoamidino, amido, alkoxy, amidoalkyl, N-monoalkylamido, N-monoarylamido, N,N-dialkylamido, N-alkyl-N-arylamido, alkylcarbonyl, alkylcarbonylalkyl, hydroxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, N-alkylsulfamyl, N-arylsulfamyl, arylsulfonyl, N,N-dialkylsulfamyl, N-alkyl-N-arylsulfamyl and heterocyclic;

d. the substituent attached at the 4-position of the pyrazole (R_3) is hydrido, alkyl, halo, haloalkyl, cyano, nitro, formyl, carboxyl, alkoxycarbonyl, carboxyalkyl, alkoxycarbonylalkyl, amidino, cyanoamidino, amido, alkoxy, amidoalkyl, N-monoalkylamido, N-monoarylamido, N,N-dialkylamido, N-alkyl-N-arylamido, alkylcarbonyl, alkylcarbonylalkyl, hydroxyalkyl, alkylthio, alkylsulfinyl, alkylsulfonyl, N-alkylsulfamyl, N-arylsulfamyl, arylsulfonyl, N,N-dialkylsulfamyl, N-alkyl-N-arylsulfamyl, heterocyclic, heterocycloalkyl and aralkyl; and

e. the 5-position of the pyrazole ring (R_4) is substituted with an aryl, cycloalkyl, cycloalkenyl or heterocyclic ring which can be optionally substituted with one or more of the following: halo,

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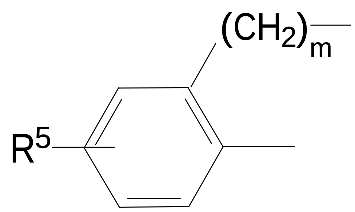
[10] ’165 patent, col. 1, ln. 10-15 (DX-033).

alkylthio, alkylsulfinyl, alkyl, alkylsulfonyl, cyano, carboxyl, alkoxycarbonyl, amido, N-monoalkylamido, N-monoarylamido, N,N-dialkylamido, N-alkyl-N-arylamido, haloalkyl, hydroxyl, alkoxy, hydroxyalkyl, haloalkoxy, sulfamyl, N-alkylsulfamyl, amino, N-alkylamino, N,N-dialkylamino, heterocyclic, nitro and acylamino; or wherein the substituents at the 3-position and 4-position of the pyrazole form:



wherein m is 1 to 3, inclusive; and wherein R_5 is one or more radicals selected from halo, alkylthio, alkylsulfinyl, alkylsulfonyl, cyano, carboxyl, alkoxycarbonyl, amido, N-monoalkylamido, N-monoarylamido, alkyl, N,N-dialkylamido, N-alkyl-N-arylamido, haloalkyl, hydrido, hydroxyl, alkoxy, hydroxyalkyl, haloalkoxy, sulfamyl, N-alkylsulfamyl, amino, alkylamino, heterocyclic, nitro and acylamino;

f. provided the substitents at R_2 and R_3 are not identical radicals selected from hydrido, carboxyl and ethoxycarbonyl; further provided that R_2 cannot be carboxyl when the R_3 is hydrido and R_4 is a phenyl; further provided R_4 is not unsubstituted thienyl when R_2 is trifluoromethyl; and further provided that R_4 is aryl substituted with sulfamyl, or R_5 is alkylsulfonyl or sulfamyl when R_1 is halo, alkyl, alkoxy, hydroxyl or haloalkyl.

29. Claim 17 of the ’165 patent specifically claims celecoxib. The ’165 patent includes 30 numbered examples and biological *in vivo* data from a rat carrageenan foot pad edema test for three compounds.

30. U.S. 5,760,068 (the “’068 patent”), is entitled “Substituted Pyrazolyl Benzenesulfonamides For the Treatment of Inflammation,” and is directed to the method of treating “inflammation or an inflammation-associated disorder” by administering a compound from the genus of compounds claimed. The genus of claim 1 is as follows:

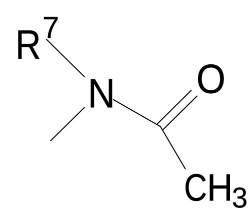
a. the heterocycle must be a pyrazole;

b. the substituent attached to the nitrogen at the 1-position of the pyrazole must be a phenyl ring which is substituted (R_1) with one or more of the following: halo, C_1-C_{10}-alkyl, and sulfamyl;

c. the substituent attached at the 3-position of the pyrazole (R_2) is selected from hydrido, C_1-C_6-haloalky, cyano, carboxy, C_1-C_6-carboxycarbonyl, C_1-C_6-alkoxy, C_1-C_6-alkylthio, aminocarbonyl. aminocarbonyl-C_1-C_6-alkyl, C_1-C_6-N-alkylaminocarbonyl, N-arylaminocarbonyl, C_1-C_6-N,N-dialkylaminocarbonyl,C_1-C_6-N-alkyl-N-aryl-aminocarbonyl, and C_1-C_6-hydroxyalkyl;

d. the substituent attached at the 4-position of the pyrazole (R_3) is selected from hydrido, C_1-C_{10}-alkyl, halo, cyano, C_1-C_6-alkoxy, C_1-C_6-hydroxyalkyl, C_1-C_6-alkylthio, and C_1-C_6-alkylsulfonyl;

e. the 5-position of the pyrazole ring (R_4) is selected from aryl-C_2-C_6-alkenyl, aryl, C_3-C_7-cycloalkyl, C_3-C_7-cycloalkenyl, and five to ten membered heterocycles, which are optionally substituted with one or more of the following: halo; C_1-C_6-alkyltho; C_1-C_6-alkylsulfinyl; C_1-C_{10}-alkyl; C_1-C_6-alkylsulfonyl; cyano; carboxyl; C_1-C_6-alkoxycarbonyl; aminocarbonyl; C_1-C_6-haloalkyl; sulfamyl; C_1-C_6-N-alkylaminocarbonyl; amino; C_1-C_6-N-alkylamino; C_1-C_6-N,N-dialkylamino; five or six membered heterocyclic; nitro; and



wherein R^7 is hydrido;

f. The genus has the further limitations that aryl means means phenyl, naphthyl, tetrahydronaphthyl, indane, biphenyl, and provided R^2 and R^3 are not identical radicals selected from hydrido, carboxyl and ethoxycarbonyl; further provided that R^2 is not carboxyl or methyl when R^3 is hydrido and when R^4 is phenyl; further provided that R^4 is not triazolyl when R^2 is methyl; further provided that R^4 is not aralkenyl when R_2 is carboxyl, aminocarbonyl or ethoxycarbonyl; further provided that R^4 is not phenyl when R^2 is methyl and R^3 is carboxyl; further provided that R^4 is not 4-chlorophenyl when R^2 is methyl and R^3 is bromo; further provided that R^4 is not unsubstituted thienyl when R^2 is trifluoromethyl; and further provided that R^4 is aryl substituted

> with sulfamyl when R^1 is phenyl not substituted with sulfamyl; and further provided the compound is not 4-[5-(3-fluro-4-methoxyphenyl)-3-(difluoromethyl)-1H-pyrazol-**l**y**l**]benzenesulfonamide; or a pharmaceutically-acceptable salt thereof.

31. The ‘068 patent claims a method of using celecoxib in claim 4.

32. The ’068 patent sets forth 260 numbered examples. The ’068 patent states that there is a preference for COX-2 selective compounds:

> The present invention preferably includes compounds which selectively inhibit cyclooxygenase II over cyclooxygenase I. Preferably, the compounds have a cyclooxygenase II IC_{50} of less than about 0.2 µM, and also have a selectivity ratio of cyclooxygenase II inhibition over cyclooxygenase I inhibition of at least 50, and more preferably of at least 100. Even more preferably, the compounds have a cyclooxygenase I IC_{50} of greater than about 1 µM, and more preferably of greater than 10 µM. Such preferred selectivity may indicate an ability to reduce the incidence of common NSAID-induced side effects.[11]

33. The ’068 patent includes: (a) biological *in vivo* data from a rat carrageenan foot pad edema test for fifteen compounds[12]; (b) biological *in vivo* data from a rat carrageenan-induced analgesia test for seven compounds[13]; and (c) COX-1 and COX-2 *in vitro* data for 53 compounds[14].

VIII. THERE WAS NO MOTIVATION TO START WITH A “SUBSTITUTED DIPHENYL HETEROCYCLE PHARMACOPHORE”

34. Each of Teva’s medicinal chemistry experts conclude that, in 1993, one of ordinary skill in the art would begin (and end) their search for a safer NSAID with a single

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[11] ’068 patent, col. 4, lines 57-67 (DX-008).

[12] ’068 patent, col. 94, ln. 20-col. 95, ln. 20 (DX-008).

[13] ’068 patent, col. 94, ln. 20-col. 95, ln.20 (DX-008).

[14] ’068 patent, col. 95, ln. 21-col.96, ln. 50 (DX-008) .

chemical class – a "substituted diphenyl heterocyle pharmacophore."[15] I do not agree. Teva's experts misrepresent the motivation of a person of ordinary skill in the art. Such a person was looking for a new and improved NSAID that lacked the gastrointestinal toxicity associated with traditional NSAIDs. COX-2 selectivity was one way to look for such a compound, but not the only way.[16] If one of ordinary skill in the art were to read the Merck '196 application, as discussed below, I do not believe that he or she would have considered the Merck '196 application important because it does not provide *in vivo* data demonstrating that the compounds are anti-inflammatory. Without such *in vivo* testing, one of ordinary skill in the art would not have had an expectation that even the specific compounds disclosed were anti-inflammatory in animals.

35. Even if we assume that one of ordinary skill in the art was looking solely for a COX-2 selective inhibitor based on *in vitro* data to serve as a lead, I do not agree that such a search would have been limited to the Merck '196 application. Published literature suggested that both DuP-697 and NS-398 were COX-2 selective.[17] I agree with Dr. Galbraith that a search would have involved a review of literature and would have identified a number of compounds of distinct structural classes.[18] I agree that there was no teaching or motivation to choose one structure (the "substituted diphenyl heterocycle[s]") over any of the other chemical structures that would have been identified.[19]

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15 Trummlitz Rep. ¶¶80, 93-98; Baker Rep. ¶¶140-145; Cooperman Rep. ¶¶124-131.

16 *See, e.g.,* Galbraith Rep. ¶19; Seibert Rep. ¶¶15-31.

17 *See, e.g.,* Prasit, "Discovery of Vioxx (rofecoxib)", Ch. 3 in "Therapeutic Roles of Selective COX-2 Inhibitors," ed. by JR Vane (2001), pp 60-75, at 60 (PFC01604084-99).

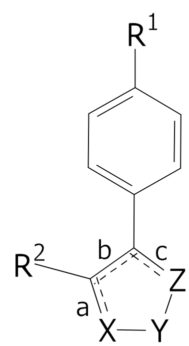
18 Galbraith Reb. Rep. ¶¶6-7.

19 Galbraith Reb. Rep. ¶8. Dr. Trummlitz, owing to his involvement in their development,
(continued...)

IX. THE MERCK ’196 APPLICATION

A. The Genus of the Merck ’196 Application[20]

36. The genus set forth in the Merck ’196 application is astoundingly broad. For thiophenes alone, I estimate that coverage was sought for 10^{18} (a billion-billion) compounds. The genus of the Merck ’196 application comprises compounds with the generic formula:



wherein,

(a) X-Y-Z-is selected from the group consisting of (depending on the placement of the double bond):
(1) $-CH_2CH_2CH_2-$,
(2) $-C(O)CH_2CH_2-$,
(3) $-CH_2CH_2C(O)-$,
(4) $-CR^5(R^{5'})-O-C(O)-$,
(5) $-C(O)-O-CR^5(R^{5'})-$,
(6) $-CH_2-NR^3-CH_2-$,
(7) $-CR^5(R^{5'})-NR^3-C(O)-$,
(8) $-CR^4=CR^{4'}-S-$,
(9) $-S-CR^4=CR^{4'}-$,
(10) -S-N=CH-,
(11) -CH=N-S-,
(12) $-N=CR^4-O-$,
(13) $-O-CR^4=N-$

19 (...continued) particularly emphasizes oxicams as an alternative class of NSAIDs with improved gastrointestinal characteristics. There was no teaching in the art to select oxicams over any other class.

20 “Merck ’196 application” means Application No. 08/082,196 filed on June 24, 1993 (PFC01597359-456).

(14) -N=CR^4-NH-;
(15) -N=CR^4-S-, and
(16) -S-CR^4=N-;
(17) -C(O)-NR^3-CR^5(R$^{5'}$)-;
(18) -R^{3}N-CH=CH- provided R^1≠-SO$_2$Me
(19) -CH=CH-NR^3- provided R^1≠-SO$_2$Me
(20) =CH-O-CH=, and
(21) =CH-NR^3-CH=,
(22) =N-S-CH=,
(23) =CH-S-N=,
(24) =N-O-CH=,
(25) =CH-O-N=,
(26) =N-S-N=,
(27) =N-O-N=,

(b) R^1 is selected from the group consisting of
(1) S(O)$_2$CH$_3$,
(2) S(O)$_2$NH$_2$,
(3) S(O)$_2$NHC(O)CF$_3$,
(4) S(O)(NH)CH$_3$,
(5) S(O)(NH)NH$_2$,
(6) S(O)(NH)NHC(O)CF$_3$,
(7) P(O)(CH$_3$)OH, and
(8) P(O)(CH$_3$)NH$_2$,

(c) R^2 is selected from the group consisting of
(1) C$_{1-6}$alkyl,
(2) C$_3$, C$_4$, C$_5$, C$_6$, and C$_7$, cycloalkyl,
(3) mono- or di-substituted phenyl wherein the substituent is selected from the group consisting of
(i) hydrogen,
(ii) halo,
(iii) C$_{1-6}$alkoxy,
(iv) C$_{1-6}$alkylthio,
(v) CN,
(vi) CF$_3$,
(vii) C$_{1-6}$alkyl,
(viii) N$_3$,
(ix) -CO$_2$H,
(x) -CO$_2$-C$_{1-4}$alkyl,
(xi) -C(R^5)(R^6)-OH,
(xii) -C(R^5)(R^6)-O-C$_{1-4}$alkyl, and
(xiii) -C$_{1-6}$alkyl-CO$_2$-R^5;
(4) mono- or di-substituted heteroaryl wherein the heteroaryl is a monocyclic aromatic ring of 5 atoms, said ring having one hetero atom which is S, O, or N, and optionally 1, 2, or 3 additionally N atoms; or

the heteroaryl is a monocyclic ring of 6 atoms, said ring having one hetero atom which is N, and optionally 1, 2, 3, or 4 additional N atoms; said substituents are selected from the group consisting of

(i) hydrogen,
(ii) halo, including fluoro, chloro, bromo and iodo,
(iii) C_{1-6}alkyl,
(iv) C_{1-6}alkoxy,
(v) C_{1-6}alkylthio,
(vi) CN,
(vii) CF_3,
(viii) N_3,
(ix) $-C(R^5)(R^6)-OH$, and
(x) $-C(R^5)(R^6)-O-C_{1-4}$alkyl;

(d) R^3 is selected from the group consisting of
(1) hydrogen,
(2) CF_3,
(3) CN,
(4) C_{1-6}alkyl,
(5) hydroxyC_{1-6}alkyl,
(6) $-C(O)-C_{1-6}$alkyl,
(7) optionally substituted
(i) $-C_{1-5}$ alkyl-Q,
(ii) $-C_{1-3}$alkyl-O-C_{1-3}alkyl-Q,
(iii) $-C_{1-3}$alkyl-S-C_{1-3}alkyl-Q,
(iv) $-C_{1-5}$ alkyl-O-Q, or
(v) $-C_{1-5}$ alkyl-S-Q,
wherein the substituent resides on the alkyl and the substituent is C_{1-3}alkyl;
(8) -Q

(e) R^4 and $R^{4'}$ are each independently selected from the group consisting of
(1) hydrogen,
(2) CF_3,
(3) CN,
(4) C_{1-6}alkyl,
(5) -Q,
(6) -O-Q;
(7) -S-Q, and
(8) optionally substituted
(i) $-C_{1-5}$alkyl-Q,
(ii) $-O-C_{1-5}$alkyl-Q,
(iii) $-S-C_{1-5}$alkyl-Q,
(iv) $-C_{1-3}$alkyl-O-C_{1-3}alkyl -Q,
(v) $-C_{1-3}$alkyl-S-C_{1-3}alkyl-Q,
(vi) $-C_{1-5}$ alkyl-O-Q,

(vii) $-C_{1-5}$ alkyl-S-Q,
wherein the substituent resides on the alkyl and the substituent is C_{1-3}alkyl, and

(f) R^5, $R^{5'}$ and R^6 are each independently selected from the group consisting of
(1) hydrogen,
(2) C_{1-6}alkyl,
or R^5 and R^6 together with the carbon to which they are attached form a saturated monocyclic carbon ring of 4, 5, 6 or 7 atoms;

(g) Q is CO_2H, CO_2-C_{1-4}alkyl, tetrazolyl-5-yl, $C(R^5)(R^6)(OH)$, or $C(R^5)(R^6)(O\text{-}C_{1-4}$a1kyl);

B. The Examples of the Merck ’196 Application

37. The Merck ’196 application has two Tables of examples. Table I contains 14 compounds.[21] For each of these compounds a synthetic method is listed and some COX-1 and COX-2 tabular data (in the form of percent inhibition) is provided. Table II contains an additional 57 compounds.[22] Neither a synthetic method nor COX-1 and COX-2 tabular data is provided for these compounds.

X. ONE OF ORDINARY SKILL IN THE ART WOULD NOT HAVE A REASONABLE EXPECTATION THAT A COMPOUND IN THE MERCK ’196 APPLICATION WOULD BE COX-2 SELECTIVE OR ANTI-INFLAMMATORY IN THE ABSENCE OF DATA FOR THAT COMPOUND

38. It is my opinion that the Merck ’196 application would not provide one of ordinary skill in the art with a reasonable basis for expecting that the compounds within the genus were COX-2 selective or anti-inflammatory because: (a) the Merck ’196 application provides tabular data for only fourteen examples from an astronomical genus comprising 10^{18} compounds; (b) within such a diverse genus, one of ordinary skill in the art would have expected the compounds to exhibit diverse activities; and (c) the Merck ’196 application lacks *in vivo* data

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21 Merck ’196 application, pp 32-34 (PFC01597359-456).

22 Merck ’196 application, pp 35-43 (PFC01597359-456).

demonstrating that any of the compounds would have anti-inflammatory activity in an animal. Overall, I find the data provided in the Merck ‘196 application does not teach that the genus of compounds are COX-2 selective or anti-inflammatory.

A. The Merck ’196 Application Provides Tabular Data for Only Fourteen Examples

39. Teva’s experts each conclude that the search for a COX-2 selective NSAID would begin with the same reference – the Merck ’196 application. It is my opinion that one of ordinary skill in the art would not have understood the Merck ’196 application to teach that all members of the genus “would be expected to be COX-2 selective”[23] based on the tabular *in vitro* data for fourteen compounds.

40. Despite the disclosure of a genus covering more than 10^{18} distinct compounds, the specification of the Merck ’196 application provides COX-1 and COX-2 percent inhibition data for only fourteen compounds. These fourteen compounds contain examples of only five heterocyclic cores (thiophene, thiazole, isothiazole, furan and furnanone) and a cyclopentanone.[24] Just one of these heterocyclic cores placed in a diaryl heterocyclic structure with substituents as listed in the application is broad enough to cover an astounding number of compounds, *e.g.*, 10^{18} for thiophenes. *In vitro* data from fourteen members of such a class provides no reasonable basis to generalize about the properties of all other members of the class.

41. Thus, it is no surprise to me that the patent examiner rejected the Merck ’196 application for the same reason – the *in vitro* data for fourteen compounds does not support a finding that all of the compounds within the genus have similar activity:

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[23] Trummlitz Rep. ¶65.

[24] Merck ’196 application, pp. 32-34 (PFC01597359-456).

> Relatively little is known regarding the activity of COX-2, and there is no predictability as to which compounds will inhibit COX-2. In such a field, the data found in the specification regarding the activity of the claimed compounds is not sufficient to enable the full scope of the invention as claimed. *Even within the limited set of compounds tested for activity, the variation of activity is so great that the data cannot be said to create the expectation that the multitude of compounds claimed will have the claimed activity.*[25]

42. The patent examiner confirms my opinion that one of ordinary skill in the art would not have expected the compounds within the genus disclosed to be COX-2 selective.

B. It Was Well Known that Heterocycles Have Different Properties

43. The expected differences between heterocycles would have left one of ordinary skill in the art with no expectation that all compounds within the genus of the Merck '196 application were COX-2 selective. It was well known in the art in 1993 that different heterocycles possess different physical, chemical and biological properties. The key aspect of lead optimization in drug discovery is often the identification and selection of the choice of heterocycles and their substituents.

44. Heterocycles have different hydrogen bonding patterns, basicity, polarity, and reactivity/stability, each of which can affect their ability to bind to the active site of the target. For example, hydrogen bonding donor and acceptor sites of an inhibitor normally require matching with complementary hydrogen bonding components of the receptor (protein) or water molecules. Similarly, hydrophobic patches on an inhibitor normally need to fit well against hydrophobic patches on the receptor. Heterocycles have other differences associated with, for example, metabolism and toxicity, which will affect a compound's ability to be used as a drug. Teva's experts provide no reference or data that one of ordinary skill in the art could rely upon to

[25] Merck '196 application, 11/12/93 Office Action, p. 6 (emphasis added) (PFC01597359-456).

form a reasonable expectation that use of any heterocycle in a diphenyl heterocycle would yield a compound that inhibited COX-2. Fundamentally, for the above reasons, one of ordinary skill in the art would not have expected that heterocycles were interchangeable – contrary to what Teva's experts suggest the Merck '196 application teaches.

45. Because of the potentially significant differences in the activity of alternative heterocycles, the literature on heterocycle synthesis, properties, uses, and activities is massive. I entered the keyword "heterocycle" into the American Chemical Society's SciFinder system and 164,563 references to journal articles and abstracts were retrieved. For 2000-2005, 109 articles are retrieved for a search on "review of heterocycle chemistry." That would seem excessive if heterocycles were generally understood to be interchangeable.

46. Differences between heterocycles are routinely seen in pharmaceutical research. In my own research on non-nucleoside inhibitors of HIV-1 reverse transcriptase, changing heterocycles shows large effects on the activities of compounds.[26] We have spent much effort synthesizing and assaying series of thiazoles, pyridines, pyrimidines and triazenes; the general patterns here are that: (a) thiazoles and pyridines are not potent enough against HIV-1; (b) the pyrimidines are very potent, but show greater cell toxicity; and (c) the triazenes have intermediate potency, but much less cell toxicity. This is a typical dance that one participates in when performing drug development using heterocycles; heterocycles are not interchangeable.

47. The views expressed by the patent examiner reiterate the well-known fact that because different heterocycles possess different physical, chemical and biological properties,

[26] Jorgensen et al., "Computer-aided design of non-nucleoside inhibitors of HIV-1 reverse transcriptase," *Bioorganic & Medicinal Chemistry Letters*, 2005, 16: 663-667 (PFC01603225-29). For related work, *see also*: Ludovici et al., "Evolution of Anti-HIV Drug Candidates. Part 3: Diarylpyrimidine (DAPY) Analogues," *Bioorganic & Medicinal Chemistry Letters*, 2001, 11(17):2235-2239, Table 1.

one of ordinary skill in the art would not have expected all of the compounds within the genus of the Merck ’196 application to be COX-2 active and selective. The patent examiner acknowledged the differences between the heterocycles and rejected Merck’s attempt to claim compounds containing each of the five-membered heterocycles disclosed in the application:

> [T]hese claims encompass species that are considered to be independent since they are unconnected in operation; one does not require the others for ultimate use and the specification does not disclose a dependent relationship between them. Moreover, *there are encompassed species that are considered to be distinct from others on the basis of their properties.*[27]

The examiner reasoned that allowing the claims “would warrant the ultimate [incorrect] conclusion that all species are patentably indistinct and a reference to one species would be considered a reference to all species.”[28]

C. The Merck ’196 Application Lacks *in vivo* Data Demonstrating That The Compounds Have Anti-inflammatory Activity

48. The lack of *in vivo* data would have precluded a conclusion that the compounds within the genus of the Merck ’196 application were anti-inflammatory. One of ordinary skill would have been aware that *in vitro* data alone does not demonstrate that the compound will have activity in an animal. *In vitro* activity, the ability of the compound to inhibit the enzyme “in glass” (a test tube), is only the first step in developing a drug. It is often the case that compounds that are good enzyme inhibitors, and have the desired activity *in vitro*, fail to demonstrate that activity *in vivo* (in a living animal). One of ordinary skill in the art would have wanted to see *in vivo* data before concluding that a compound had certain activity in an animal.

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[27] Merck ’196 application, 11/12/93 Office Action, p. 3 (emphasis added) (PFC01597359-456).

[28] Merck ’196 application, 11/12/93 Office Action, p. 4 (PFC01597359-456).

49. The Merck '196 application does not contain any *in vivo* data demonstrating that the compounds possessed anti-inflammatory properties in an animal. The Merck '196 application would not teach one of ordinary skill in the art that the broad genus of compounds disclosed were anti-inflammatory compounds, even though it asserts they are anti-inflammatory, because *in vitro* enzyme inhibitors do not necessarily exhibit similar activity *in vivo*.

50. The Examiner confirmed my opinion and acknowledged that the lack of *in vivo* data showed that there was no evidence that the compounds had anti-inflammatory activity:

> In an informal interview Examiner Gabalin clarified that with regard to the compounds and their use as anti-inflammatory agents, she is concerned that there is insufficient proof that inhibition of COX-2 would translate to anti-inflammatory activity.[29]

In response to this concern, inventors of the Merck '196 application included *in vivo* data from a rat paw edema assay, "demonstrating that applicants [sic.] compounds are useful anti-inflammatory agents,"[30] in their next patent application. I understand that the patent application containing the *in vivo* data was not filed until January 10, 1994.[31]

XI. TEVA'S CONSTRUCTION OF A PHARMACOPHORE IS NOT SUPPORTED BY THE MERCK '196 APPLICATION

51. Even if, contrary to my opinion expressed above, one of ordinary skill in the art would have understood the Merck '196 application to have disclosed a genus of compounds where each member of the genus could reasonably be expected to be COX-2 selective, one of ordinary skill in the art would not have generated the pharmacophore set forth

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[29] Merck '196 application, 2/22/98 Express Abandonment, p. 2 (PFC01597359-456).

[30] Merck '196 application, 2/22/98 Express Abandonment, p. 3 (PFC01597359-456).

[31] Merck '196 application, 2/22/98 Express Abandonment, p. 1 (PFC01597359-456).

by Teva's experts. If, contrary to my opinion, one of ordinary skill in the art would have been motivated to create a pharmacophore (herein referred to as the "Teva Pharmacophore"), one of ordinary skill in the art would have relied primarily on the examples for which data was provided.

52. The Teva Pharmacophore, which leaves many of the substituents undefined, would encompass another astronomical number of compounds. In order to generate the Teva Pharmacophore, Teva's experts make the following assumptions which, as discussed below, cannot be supported by the Merck '196 application or any other data available to one of ordinary skill in the art in 1993, and are at odds with actual data obtained by Searle:

a. "The identity of the five-membered ring . . . is not significant to the activity of the compound as a COX-2 selective anti-inflammatory"[32]

b. "[T]he position of the heteroatoms in the five-membered heterocycle is not significant to the activity of the compound as a COX-2 inhibitor"[33]

c. The aryl rings must be "phenyl groups" and can be in any position on the heterocycle ring as long as they attached to "adjacent atoms"[34]

d. "[T]he use of a sulfamyl or methylsulfonyl on phenyl 'A' is critical" to achieving COX-2 activity and selectivity"[35]

e. The sulfamyl and methyl sulfone (methylsulfonyl)substituents are interchangeable "for achieving COX-2 selectivity when used with any five-membered heterocycle[36]

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[32] Baker Rep. ¶132; *see also* Cooperman Rep. ¶62.

[33] Baker Rep. ¶132; *see also* Cooperman Rep. ¶67.

[34] Baker Rep. ¶133; *see also* Cooperman Rep. ¶¶57-59.

[35] Baker Rep. ¶144.

[36] Baker Rep. ¶134; *see also* Trummlitz Rep. ¶82.

f. The "optional" substituent on the heterocycle and the phenyl ring are not essential for potency or selectivity[37]

g. The "optional" substituents should be small[38]

53. As discussed below, one of ordinary skill in the art would not draw these conclusions. From the Merck '196 application, it is my opinion that if, contrary to my opinion expressed above, one of ordinary skill in the art would make generalizations as to the properties of compounds within a broad genus based on data from only fourteen compounds, one would conclude as follows:

A. The Only Heterocycles That the Merck '196 Application Discloses As Potentially COX-2 Selective Are the Eight Heterocycles in Tables I and II

54. The conclusion by Dr. Baker that the "identity of the five-membered ring heterocycle . . . is not significant to the activity of the compound as a COX-2 selective anti-inflammatory"[39] is not supported by the Merck '196 application. Table 1 of the Merck '196 application contains fourteen examples comprising five heterocycles (thiophene, furan, furanone, thiazole, and isothiazole) and cyclopentanone. Considering the examples in Table II (unsupported by tabular data) only adds three additional heterocycles (pyrrole, maleamide and a dihydropyrrolone). Thus, even if one of ordinary skill in the art would have thought that tabular data for just fourteen compounds created an expectation that all diphenyl compounds containing the ring systems in the examples were COX-2 selective (which it does not), the extension of the pharmacophore beyond the nine rings in the examples (eight heterocycles and one cyclopentene) is unsupported.

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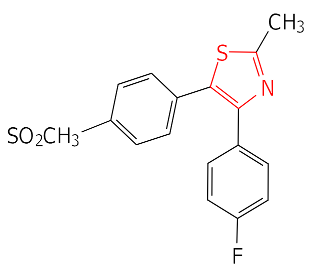
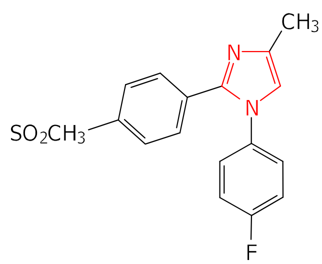
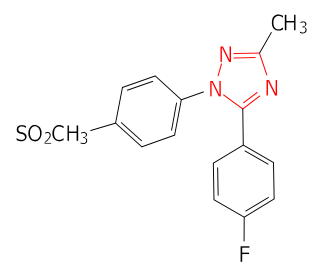
37 Cooperman Rep. ¶88-89.

38 Baker Rep. ¶135.

39 Baker Rep. ¶132; *see also* Cooperman Rep. ¶67.

55. As discussed above, due to the known and expected differences between heterocycles, one of ordinary skill in the art would have expected that the identity of the five-membered heterocycle would affect COX-2 activity and selectivity. In fact, switching the heterocycle can result in changes in COX-2 activity. For example, Searle tested the four compounds below (each of which are within the Teva Pharmacophore). The clear difference among these compounds is the identity of the five-membered heterocycle. As shown below, although the thiazole (MCP-179074) was COX-2 selective, the pyrazole (SC-59494) and the triazole (SC-58043) did not have detectable COX-2 activity at concentrations as high as 100µM.

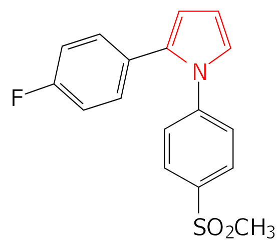
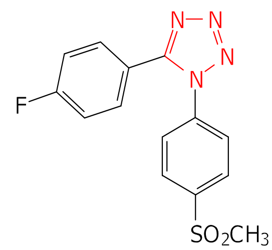
		
MCP-179074[40]	**SC-59494**[41]	**SC-58043**[42]
COX-1 IC50: >100µM	COX-1 IC50: >100µM	COX-1 IC50: >100µM
COX-2 IC50: 0.116µM	COX-2 IC50: >100µM	COX-2 IC50: >100µM

Similarly, Searle tested SC-57126 (a pyrrole within the Teva Pharmacophore) and found the compound to be COX-2 selective. However, after simply changing the heterocycle to a tetrazole (another five-membered heterocycle not disclosed by the Merck ’196 application), the resulting compound, SC-57855, had no detectable COX-2 activity.

40 PFC01592069; PFC01552789; PFC01554299.

41 PFC01592210; PFC01230024; PFC01555722.

42 PFC01592109; PFC00668855; PFC01228682; PFC01554299.

	
SC-57126[43]	**SC-57855**[44]
COX-1 IC50: >100µM	COX-1 IC50: >100µM
COX-2 IC50: 0.511µM	COX-2 IC50: >100µM

Additional compounds within the Teva Pharmacophore that demonstrate that the identify of the heterocycle can have a great effect on COX-2 activity are set forth in Exhibit 1. One of ordinary skill in the art would have expected small changes could have a significant effect on activity.

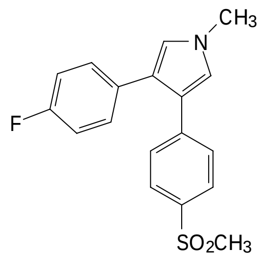
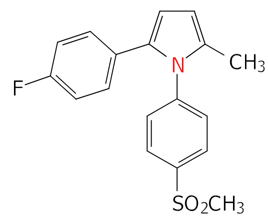
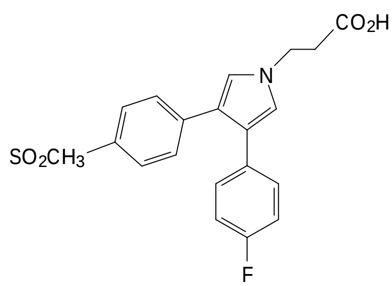
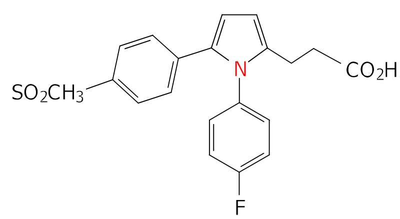
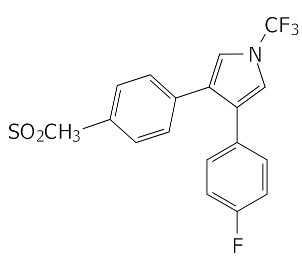
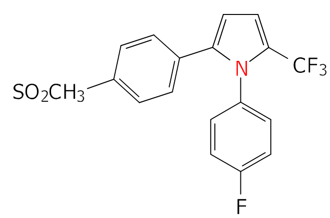
B. Conclusions Drawn By Teva's Experts With Respect to the Heteroatoms Do Not Follow From the Merck '196 Application

56. Dr. Baker states that "the position of the heteroatoms . . . is not significant to the activity of the compound as a COX-2 selective anti-inflammatory" and "any heteroatom can appear at any position in the heterocycles."[45] It is impossible to draw these conclusions based on the data from only fourteen compounds. Furthermore, as shown below, these conclusions are often not correct. Searle scientists tested several compounds that differed from compounds within the genus of the Merck '196 application by their attachment of a phenyl ring to the heteroatom. Significantly, these compounds had no detectable COX-2 activity.

43 PFC01592078; PFC01228762; PFC01554299.

44 PFC01592095; PFC00316100; PFC01554299.

45 Baker Rep. ¶ 132.

Compound Within Genus of the Merck '196 Application	**Corresponding Compound Tested By Plaintiffs (Heteroatom in Red)**
	 **SC-56975**[46] COX-1 IC50: >100µM COX-2 IC50: >100µM
	 **SC-57484**[47] COX-1 IC50: >100µM COX-2 IC50: >100µM
	 **SC-58740**[48] COX-1 IC50: >100µM COX-2 IC50: >100µM

46 PFC01592078; PFC01228721; PFC01552763.

47 PFC01592083; PFC01228769; PFC01554299.

48 PFC01592158; PFC01228879; PFC01554690.

Additional compounds within the Teva Pharmacophore that demonstrate that the position of the heteroatom can have a significant effect on COX-2 activity are set forth in Exhibit 2. One of ordinary skill in the art would have expected small changes could have a significant effect on activity.

57. Neither the Merck ’196 application nor Teva’s experts explain when one would be correct in expecting COX-2 selectivity and when, as shown above, one would be wrong.

58. The genus of the Merck ’196 application prohibits attaching the phenyl rings to a heteroatom. This is inconsistent with the claimed insignificance of the identity of the heterocycle and the position of the heteroatoms. Thus, one of ordinary skill in the art would have had no basis for concluding that the positions of the heteroatoms are not relevant to COX-2 activity. One of ordinary skill in the art would know that the nature of the heterocycles, including the specific positioning of the heteroatoms, modulates activities.

59. Additionally, in order to draw conclusions about how possible changes in the chemical structure of a compound will affect the compound’s activity one of ordinary skill in the art would require an extensive amount of data which is absent from the Merck ’196 application. Developing the SAR for a single heterocycle would require, at a minimum, synthesizing and measuring the activity of many compounds containing the heteroatom(s) in alternative locations and with different substituents on the ring. In our and others’ anti-HIV-1 efforts it has been normal to synthesize and assay 20-50 compounds within a single heterocycle series.[49] It is straightforward to write down more than 50 aromatic five-membered heterocycles,

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[49] Jorgensen et al., “Computer-aided design of non-nucleoside inhibitors of HIV-1 reverse transcriptase,” *Bioorganic & Medicinal Chemistry Letters*, 2005, 16: 663-667 (PFC01603225-29).

plus another 50 non-aromatic ones, for the Teva Pharmacophore. To make valid conclusions covering all five-membered heterocycles would require synthesizing and developing SAR for thousands or tens of thousands of compounds. The data in the Merck ’196 application are grossly inadequate to draw broad SAR conclusions covering all five-membered heterocycles as Teva’s experts suggest.[50]

C. The Merck ’196 Application Teaches More Than Phenyl Rings and Limits the Location of the Rings

60. Teva’s experts state that the Merck ’196 application teaches that the aryl rings must be phenyl and the phenyl groups can be attached at any position of the heterocycle, as long as they are on “adjacent atoms.”[51] I disagree. First, in the Merck ’196 application, an example of Table I (which contains the only examples for which there is tabular data) teaches that one ring could be replaced by a saturated cyclohexane ring. Second, the examples of the Merck ’196 application do not teach, and the genus set forth in the Merck ’196 application prohibits,[52] attaching the phenyl rings to a heteroatom. Thus, at best, the Merck ’196 application teaches attaching either a phenyl or a saturated cyclohexane ring to adjacent non-heteroatom positions of the heterocycle. Importantly, based on this limitation, if one of ordinary skill in the art was trying to learn something from the Merck ‘196 application, he/she would not be motivated to make any of the compounds within the patents-in-suit that require that an aryl ring must be attached to the nitrogen at the 1-position of the pyrazole ring.

61. The compounds from Searle’s research program, set forth in Exhibit 3, demonstrate that the placement of adjacent phenyl rings on the heterocycle of compounds within

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50 Trummlitz Rep. ¶¶71-75; Cooperman Rep. ¶¶62-66; *see also* Baker Rep. ¶¶144, 147.

51 Baker Rep. ¶133; Trummlitz Rep. ¶73; Cooperman Rep. ¶57.

52 Merck ’196 application, p. 3 (PFC01597359-456).

the Teva Pharmacophore can have a significant effect on COX-2 activity. One or ordinary skill in the art would have expected that small changes could have a significant effect on activity.

D. There Is No Basis for Concluding that a Methyl Sulfone and a Sulfamyl Are "Critical" to COX-2 Activity

62. There is no support for Dr. Baker's statement that "a person of ordinary skill in the art would recognize that with regard to the pharmacophore taught in the Merck '196 application . . . the use of the sulfamyl or methyl sulfone on phenyl 'A' is critical."[53] As stated above, conclusions such as this require extensive SAR data, which is absent from the Merck '196 application. At the very least, a conclusion that the methyl sulfone and sulfamyl are critical for COX-2 activity and selectivity would require the synthesis and testing of numerous diverse compounds that possessed one of these substituents. It would also require synthesis and testing of many compounds that did not possess either substituent, and a demonstration that those compounds did not have COX-2 activity and selectivity. The data presented do not preclude the possibility that these groups make no contact with the COX enzymes in their complexes. Secondly, Table I also contains an example with an $SO_2NHC(O)CF_3$ group. Though the fate of this example compound in an *in vitro* assay is uncertain, it is neither a sulfamyl or a methyl sulfone group and the compound is active. This would suggest that these two substituents are not "critical."

E. The Merck '196 Application Does Not Teach that Methyl Sulfone and Sulfamyl Are Interchangeable for Achieving COX-2 Selectivity for Non-Disclosed Five-Membered Heterocycles

63. Based on the data in the Merck '196 application, one of ordinary skill in the art would not (and could not) conclude that the methyl sulfone and sulfamyl are interchangeable under any circumstances, let alone in any diphenyl heterocycle. As explained

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53 Baker Rep. ¶144.

above, one cannot make conclusions about the activity that substituents may confer on a particular heterocycle-containing structure without synthesizing and testing representative compounds containing the heterocycle. At a minimum, in order to make this conclusion with respect to a single heterocycle, one would have to synthesize and test compounds containing the heterocycle, in combination with methyl sulfone, sulfamyl and other substituents. A change in the heterocycle can cause a shifting of the molecule in the inhibitor binding site, which can lead to variations in the effects of the substituents.

64. The Merck '196 application falls far short of providing the data necessary to make this conclusion with respect to the heterocycles set forth in the examples, let alone those disclosed in the genus or, broader still, all five-membered heterocycles. Of the fourteen examples, there are only two examples of a single heterocycle (a furanone) that show compounds that are identical except for the methyl sulfone or sulfamyl.[54] Based on this very limited disclosure, one of ordinary skill in the art would not understand the Merck '196 application to teach that the methyl sulfone and sulfamyl are interchangeable among all furanones, and certainly not among any compounds containing other heterocyclic cores.

65. Furthermore, one of ordinary skill in the art would not have thought that the methyl sulfone and sulfamyl substituents would result in compounds having the same COX-2 activity for at least the reasons below:

66. First, the prior art in the Fujisawa references[55] taught away from the interchangeability of methyl sulfone and sulfamyl on a pyrazole. In 1991, Fujisawa filed the application leading to WO 91/19708, which claimed diphenyl thiophene compounds that were

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54 *See* Merck '196 application, p. 33, examples 9 and 10 (PFC01597359-456).

55 The "Fujisawa references" means European Patent Applications 0 554 829A2 (DX-040) and 0 418 845 A1 (PFC01603002-72).

useful as anti-inflammatory agents. The patent reference discloses a genus of compounds wherein one of the phenyl rings could be substituted by, among other things, a methyl sulfone or a sulfamyl. In a later patent, EP0554829A2, the same inventors claimed anti-inflammatory diphenyl pyrazole compounds but listed only the methyl sulfone among the possible substituents that could be attached to the phenyl ring. One of ordinary skill in the art would have been aware of both Fujisawa references and could easily have understood them to teach: (a) that the methyl sulfone and sulfamyl are not interchangeable with respect to heterocycles in general and pyrazoles in particular; and (b) that sulfamyl groups may have some unspecified liability.

67. Second, methyl sulfone and sulfamyl were not known to be bioisosteres. Substituents are isosteres if they have the same number of valence electrons.[56] Isosteres are generally not expected to have the same biological activity. However, when isosteres are determined, based on testing, to have similar biological activity, they are referred to as bioisosteres with respect to that activity.[57] Although I agree that, in 1993, one of ordinary skill in the art would have considered the methyl sulfone and sulfamyl substituents to be isosteres, they would not have considered them to be bioisosteres.[58]

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56 Patani, "Bioisosterism: A Rational Approach in Drug Design," *Chem. Rev.*, 1996, 96: 3147-3176, 3148 (PFC01606414-43); Korolkovas, "Essentials of Molecular Pharmacology," John Wiley & Sons, 1970, pp. 54-59 (PFC01603261-67); Foye et al, "Principles of Medicinal Chemistry," 4th Ed., 1995, pp. 40-49.

57 Patani, "Bioisosterism: A Rational Approach in Drug Design," *Chem. Rev.*, 1996, 96: 3147-3176, 3148 (PFC01606414-43); Korolkovas, "Essentials of Molecular Pharmacology," John Wiley & Sons, 1970, pp. 54-59 (PFC01603261-67); Foye et al, "Principles of Medicinal Chemistry," 4th Ed., 1995, pp. 40-49.

58 Korolkovas, "Essentials of Medicinal Chemistry," Second Edition, John Wiley & Sons, 1988, pp. 78-83 (PFC01603261-67); Foye et al, "Principles of Medicinal Chemistry," 4th Ed., 1995, pp. 40-49.

68. Third, methyl sulfone and sulfamyl have notably different hydrogen bonding patterns. The methyl sulfone can only serve as a hydrogen-bond acceptor via its oxygen atoms, while a sulfamyl group is both a good hydrogen-bond acceptor and a strong hydrogen-bond donor (via its NH_2 group). This difference is expected to affect a variety of properties, including binding to the enzyme and, for example, solubility.

F. There is No Basis For Concluding That the "Optional" Substituents Are Not "Critical" For Activity

69. First, there is no basis in the Merck '196 application for concluding that the "optional" substituents that can be attached to the heterocycle and phenyl "B" are not critical for activity. As stated above, there is simply not enough data on which to draw this conclusion. In fact, one would not know whether or not they were, as Teva's experts say, "optional."[59] As demonstrated in Exhibits 4 and 5, the identity, position and number of the "optional" heterocycle substituents and "optional" phenyl "B" substituent, respectively, have a great effect on COX-2 activity of compounds within the Teva Pharmacophore.

70. Second, Teva's experts, having relied strictly on the examples in Tables I and II to limit the pharmacophore to *adjacent diphenyl rings* and a methyl sulfone or a sulfamyl (as opposed to the numerous other substituents permitted by the genus of the Merck '196 application), ignore the teachings of the examples in Tables I and II with respect to the "optional" substituents.

71. With respect to the "optional" substituent on the heterocycle, the examples of Table I of the Merck '196 application teach that the heterocycles can either be unsubstituted or contain one of the following five substituents:

a. hydroxyisopropyl ($-C(CH_3)_2OH$)

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59 Trummlitz Rep. ¶85; Cooperman Rep. ¶69; Baker Rep. ¶164.

b. isopropyl (-$CH(CH_3)_2$)
c. carboxylic acid (-CO_2H)
d. methyl (-CH_3)
e. *gem*-dimethyl (-$(CH_3)_2$)

72. Even if one of ordinary skill in the art would include the examples in Table II, only one additional substituent is taught – a trifluoromethyl (-CF_3). If the reasoning of Teva's experts were applied consistently, one of ordinary skill in the art would understand that the "optional" substituents that can be attached to the heterocycle should be limited to those taught in the examples.

73. Similarly with respect to the "optional" substituent attached on phenyl "B", there is no basis from which to conclude that the "optional" substituent does not affect COX-2 activity, and in fact one of ordinary skill in the art, based on the examples in Table I for which there are tabular data, may have concluded the opposite. In Table I of the Merck '196 application, phenyl B has a para-fluoro substituent in 12 of the 13 substituted examples, and a carboxylic acid in the other. Following the logic that Teva's experts used to conclude the sulfamyl and methyl sulfone were "critical", it could be that a para-fluoro or a carboxylate group was "critical". Furthermore, even considering all of the examples in Tables 1 and 2, one of ordinary skill in the art would conclude that the "optional" phenyl "B" substituent should be selected from one of the following nine substituents:

a. hydrogen (-H)
b. fluoro (-F)
c. chloro (-Cl)
d. bromo (-Br)
e. methoxy (-OMe)
f. carboxylic acid (-CO_2H)
g. acetic acid (-CH_2CO_2H)
h. hydroxyisopropyl (-$C(CH_3)_2OH$)
i. 2-propionic acid (-$CH(CH_3)CO_2H$)

G. No Conclusions Can Be Drawn Regarding the Size of the "Optional" Substituents

74. Dr. Baker's statement that these "optional substituents should be relatively small so as not to perturb the binding of the pharmacophore to the enzyme" is not supported by the Merck '196 application.[60] There is no teaching in the Merck '196 application regarding the structure of the binding site of the COX-2 enzyme[61] or how the compounds disclosed bind to the COX-2 enzyme. Thus, it is impossible to conclude from the Merck '196 application how the size or shape of the optional substituents would impact the ability of the compounds to bind to the enzyme and what effect that would have on the activity of the compound.

75. Moreover, as stated earlier, even small structural changes to a compound can produce differences in activity.

H. The "Pharmacophore" Taught By the Examples of the Merck '196 Application

76. Thus, even if, contrary to my opinion, one were to: (a) imagine that all of the compounds within the genus were COX-2 selective; (b) attempt to create a pharmacophore; and (c) rely on the examples from both Tables I and II from the Merck '196 application to create such a pharmacophore, the pharmacophore that a person of ordinary skill in the art would have created is as follows:

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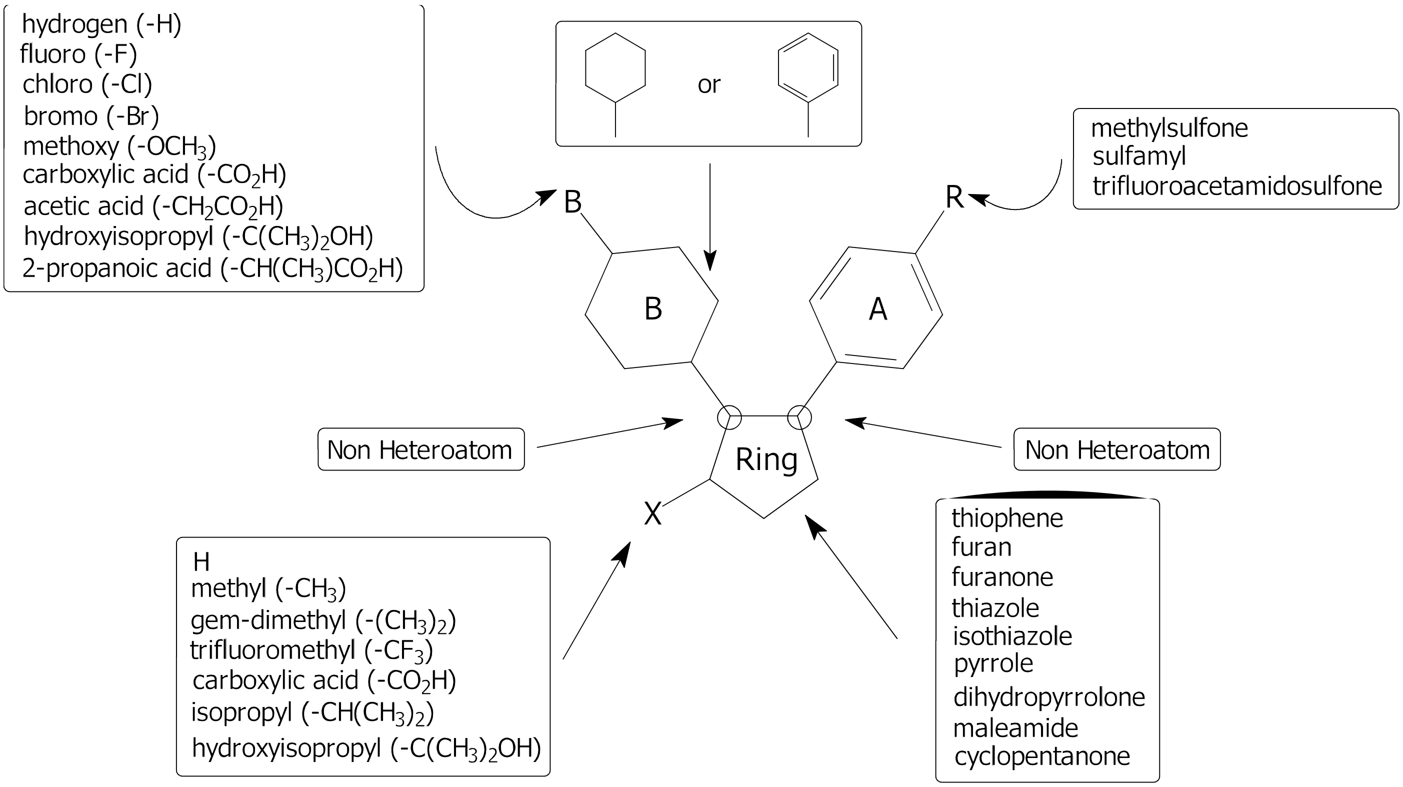
60 Baker Rep. ¶135.

61 The structure of the COX-2 enzyme was not known until 1996. *See* Kurumbail et al., "Structural Basis for Selective Inhibition of Cyclooxygenase-2 by Anti-inflammatory Agents," *Nature*, 1996, 384: 644-648 (PFC00238777-81).



77. This pharmacophore does not encompass celecoxib or any of the compounds claimed in the patents-in-suit. Even if expanded to encompass all heterocycles and substituents taught by the entire genus of the Merck ’196 application, the pharmacophore would not cover any of the compounds in the patents-in-suit because the Merck ’196 application (a) does not teach a pyrazole and (b) teaches away from attaching a phenyl ring to the heteroatom.

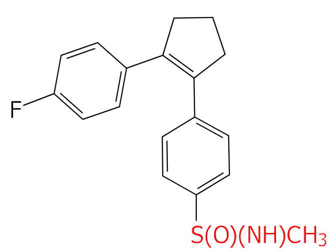
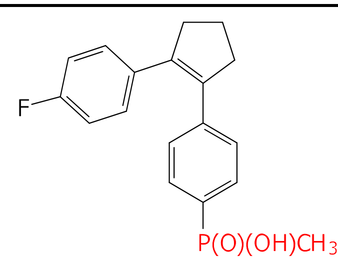
XII. THERE IS NO EXPECTATION THAT COMPOUNDS OF THE TEVA PHARMACOPHORE WOULD BE COX-2 SELECTIVE

78. Even assuming that the Merck ’196 application actually disclosed the Teva Pharmacophore, one of ordinary skill in the art would not have had an expectation that all compounds within the Teva Pharmacophore had COX-2 activity. Owing to the possibilities for heterocycles (>50) and optional small substituents on the phenyl group (ca. 30 x 3 (ortho, meta,

para) possibilities for mono-substituted; 30 x 30 x 6 possibilities for di-substituted; etc.), the pharmacophore set forth by Teva's experts encompasses millions of compounds.

79. It would have been well-known in 1993 (as it is today) that even small changes in chemical structure can have a great effect on activity.[62] Based on this knowledge, one of ordinary skill in the art would not have expected the millions of compounds encompassed by the Teva Pharmacophore to all be COX-2 selective.

80. The fact that one of ordinary skill in the art would not reasonably expect compounds within the genus taught by the Merck '196 application to be COX-2 selective is borne out by SAR data from Searle. Compounds containing other R-substituents disclosed in the Merck '196 application ($-S(O)(NH)CH_3$ and $-P(O)(CH_3)OH$) with cyclopentenes (also disclosed in the Merck '196 application) resulted in compounds with no detectable COX-2 activity. This demonstrates that one of ordinary skill in the art would not have understood the examples of the Merck '196 application to teach that the entire genus of the application was COX-2 selective.

	
SC-58711[63]	**SC-59306**[64]
COX-1 IC50: >100µM	COX-1 IC50: >100µM

62 *See, e.g.*, Korolkovas, "Essentials of Molecular Pharmacology," John Wiley & Sons, 1970, pp. 8-11, 41 (PFC01603261-67); Song et al., "Synthesis, Structure-Activity Relationships, and In Vivo Evaluations of Substituted Di-*tert*-butylphenols as a Novel Class or Potent, Selective, and Orally Active Cyclooxygenase-2 Inhibitors. 2. 1,3,4- and ,2,4-Thiadiazole Series" *J. Med. Chem.*, 1999, 42:1161-1169, Table 1.

63 PFC01592155; PFC01554656; PFC01554690; PFC01568079.

64 PFC01592195; PFC01563973; PFC01555654; PFC01554676.

COX-2 IC50: >100µM	COX-2 IC50: >100µM

81. As demonstrated in Exhibit 6, if one ignores the requirement from the Merck ’196 application that the phenyl rings not be attached to the heteroatom on the heterocycle, as Teva’s experts do, one can find dozens of compounds within the Teva Pharmacophore, and containing the eight heterocycles disclosed in the examples of the Merck ’196 application, that do not have detectable COX-2 activity at concentrations as high as 100µM in Searle’s assays. This data confirms and evidences what one of ordinary skill in the art would have already known – slight changes in chemical structure often have a significant and unpredictable impact on biological activity.

82. When considering Searle’s data on these compounds, it is important to keep in mind that Searle scientists were generally trying to find compounds that were COX-2 selective and therefore generally only tried to synthesize compounds that they expected to be COX-2 selective based on their large and growing body of SAR data. Nevertheless, because of the trial-and-error nature of drug development, Searle ended up synthesizing numerous compounds that lacked detectable COX-2 activity.

XIII. THERE IS NO MOTIVATION TO SYNTHESIZE HETEROCYCLES NOT DISCLOSED BY THE MERCK ’196 APPLICATION

83. Acknowledging that the Merck ’196 application does not disclose pyrazoles, Teva’s experts nevertheless attempt to craft a motivation to make pyrazole compounds. In order to do so, Teva’s experts assume that one of ordinary skill in the art would have:

a. “looked for components known in the art (as of November 30, 1993) that could be used to make new COX-2 selective compounds within the pharmacophore.”[65]

b. “started by looking for heterocycles that . . . are not taught in the Merck ’196 application” in order to make compounds not “encompassed” by the Merck ’196 application[66]

c. been motivated to choose a pyrazole over all other non-disclosed five-membered heterocycles based on reviewing the literature.

d. found the Fujisawa references and (i) been motivated to make pyrazole compounds that retained other features of the Teva Pharmacophore and (ii) expected the compounds to be COX-2 selective.

84. As discussed below, these assumptions are not supported. From my review of the relevant literature, I conclude:

A. There Is No Motivation to Synthesize Compounds Outside the Genus of the Merck ’196 Application

85. There is no motivation in the Merck ’196 application to synthesize compounds that do not fall within the genus of the application, nor is there the general expectation that, if one did so, the compounds would have COX-2 activity or selectivity.[67] Absent any motivation or reasonable expectation of success, Teva’s experts nevertheless conclude that “a person of ordinary skill in the art would have looked for components known in the art (as of November 30, 1993) that could be used to make new COX-2 selective compounds

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65 Baker Rep. ¶146.

66 Baker Rep. ¶¶147-148; *see also* Cooperman Rep. ¶¶91-93.

67 As stated above, the patent examiner explicitly found that, based on the examples in the Merck ’196 application (PFC01597359-456), one of ordinary skill in the art would <u>not</u> have had a reasonable expectation that the genus of the application was COX-2 active and selective. (Merck ’196 application, 11/12/93 Office Action, p. 6.) Not having this expectation for the genus, one would obviously not have any expectation that compounds outside the genus would have similar COX-2 activity.

within the pharmacophore."[68] In so doing, Teva's experts opine that one of ordinary skill in the art "would have started by looking for heterocycles that . . . are not taught in the Merck '196 application" in order to make compounds not "encompassed" by the Merck '196 application.[69] Teva's theory that one of ordinary skill in the art would be motivated to avoid the genus of the Merck '196 application provides neither a motivation to make any particular compound nor a reasonable expectation that such compounds (not within the genus of the Merck '196 application) would be COX-2 selective.

B. There Is No Teaching to "Evade" the Merck '196 Application by Changing the Heterocycle

86. Even assuming that one would be motivated to select compounds within the Teva Pharmacophore to create compounds that were not "encompassed" by the Merck '196 application, there is no suggestion in the application or anywhere else to make the selection described by Teva's experts. To begin with, there is no reason given as to why varying the heterocycle should be selected as the way to avoid the Merck '196 application, as opposed to changing any other part of the pharmacophore. One could have just as easily opted to change other substituents such as the phenyl rings, the position of the phenyl rings, or any of the substituents on the phenyl rings of the heterocycle.

87. One of ordinary skill in the art could have chosen to change the R-substituent. Teva's experts give no reason why one of ordinary skill in the art would understand from the Merck '196 application that they could use any heterocycle, including heterocycles not disclosed by the application, yet would never think that other substituents could be used in place of the sulfamyl or methyl sulfone. Alternative sulfone and sulfonamide groups,

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68 Baker Rep. ¶146.

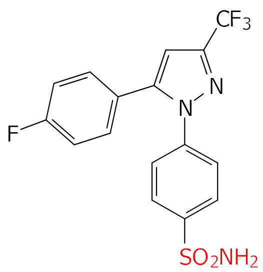
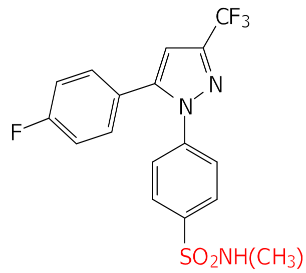
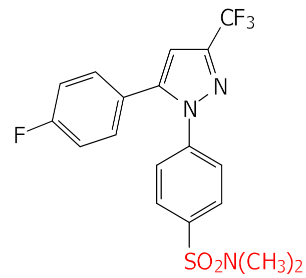
69 Baker Rep. ¶¶147-148; *see also* Cooperman Rep. ¶¶91-93.

and amide, sulfoxide and tertiary alkyl groups would also be reasonable possibilities. Again, there is no data in the Merck ’196 application demonstrating that the sulfamyl or methyl sulfone groups are essential.

88. Substituting another substituent for the sulfamyl or methyl sulfone would have created compounds that retained one of the heterocycles disclosed in the Merck ’196 application, but would not have been “encompassed” by the Merck ’196 application because of the differing R-substituent. This would have fulfilled the criteria set forth by Teva’s experts for “avoiding” the Merck ’196 application; yet, inexplicably, they ignore this possibility. Nevertheless, with compounds containing different heterocycles, one of ordinary skill in the art would not have had any expectation that all diphenyl heterocycles with replacement of the sulfamyl and methyl sulfone would have COX-2 activity or selectivity.

89. For example, since each of the three R-substituents in the examples of the Merck ’196 application is a sulfonyl derivative, and the Merck ’196 application does not teach that the sulfamyl or methyl sulfone are required for activity, it is just as likely one of ordinary skill in the art would have chosen to change of the R-substituent to an alternative sulfonamide group. This would have allowed them to get outside the genus of the Merck ’196 application while staying close to the teaching of the sulfamyl and methyl sulfone. Since the examples specifically taught a primary sulfonamide (a sulfamyl, SO_2NH_2), one of ordinary skill in the art may have tried a secondary sulfonamide ($SO_2NH(CH_3)$) or a tertiary sulfonamide ($SO_2N(CH_3)_2$). As demonstrated in the table below, when attached to a pyrazole – the heterocyclic ring claimed in the patents-in-suit – neither of these substituents resulted in compounds with a detectable

COX-2 IC_{50} value. This would have been unexpected and further demonstrates that very small changes can have drastic effects on a compound's COX-2 activity.[70]

		
SC-58500[71]	**SC-58612[72]**	**SC-58613[73]**
COX-1 IC50: >20µM	COX-1 IC50: >100µM	COX-1 IC50: >100µM
COX-2 IC50: >0.041µM	COX-2 IC50: >100µM	COX-2 IC50: >100µM

C. There Was No Motivation to Exclude Other Non-Disclosed Five-Membered Heterocycles

90. Even if the Merck '196 application had motivated one to change the heterocycle to another, undisclosed, five-membered heterocycle, there was no motivation in the Merck '196 application (or anywhere else) to choose a pyrazole rather than some other five-membered heterocycle not disclosed within the Merck '196 application.

91. Furthermore, one of ordinary skill in the art would have had no expectation that the undisclosed heterocycles would result in compounds that were COX-2 active and selective. For example, as set forth above, Searle synthesized compounds within the Teva Pharmacophore containing two five-membered heterocycles that were not disclosed by the

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70 Additional examples of sulfonamide and sulfone analogs from Searle's research program are set forth in Exhibits 7 and 8, respectively.

71 PFC01592140; PFC0288716; PFC01229614; PFC1554608; PFC01554631.

72 PFC01592149; PFC0288716; PFC01229626; PFC01554631.

73 PFC01592149; PFC0288716; PFC01229626; PFC01554631.

Merck ’196 application – a triazole (SC-58043) and a tetrazole (SC-57855). Both compounds had no detectable COX-2 activity in plaintiffs’ assay. This is consistent with the statement by the patent examiner who rejected the Merck ’196 application that heterocycles “are considered to be distinct from others on the basis of their properties.”[74]

D. The Fujisawa References Provide Neither Motivation to Make a Pyrazole nor an Expectation of Success

92. There is no motivation in the Merck ’196 application or the Fujisawa references to combine the pyrazole taught in the Fujisawa references with certain teachings of the Teva Pharmacophore (allegedly taught in the Merck ’196 application) nor is there an expectation that the resulting compounds would be COX-2 active or selective. Even if one of ordinary skill in the art conducted a literature search for heterocycles not disclosed by the Merck ’196 application and found the Fujisawa references, it is my opinion that the Fujisawa references teach away from using the pyrazole heterocycle in combination with the Merck ’196 application in the particular way described by Teva’s experts for the following reasons.

93. First, the Fujisawa references do not teach that the compounds they disclose are COX-2 active or selective. There is no suggestion in the Fujisawa references that the millions of compounds they disclose are COX-2 selective, nor is there a suggestion that the compounds are gastric sparing. Without such a teaching, one of ordinary skill in the art would not have (a) expected the compounds in the Fujisawa references to possess COX-2 activity or selectivity, (b) been motivated to use a single component of those compounds – the pyrazole – with the Teva Pharmacophore, or (c) had an expectation that the resulting compounds would be

[74] Merck ’196 application, 11/12/93 Office Action, p. 3 (PFC01597359-456).

COX-2 selective or active. Moreover, as discussed above, Fujisawa's thiophene reference in conjunction with Fujisawa's pyrazole references teaches away from using a pyrazole.[75]

94. Second, the Fujisawa references teach that the compounds disclosed have COX-1 activity. It was well known in the art in 1993 that COX-1 was the cyclooxygenase enzyme responsible for the production of thromboxane in platelets.[76] Thus, if one were to inhibit thrombosis (the act of clotting mediated by platelet aggregation), it would be expected that one was inhibiting COX-1, not COX-2. The Fujisawa references expressly state that the compounds have "antithrombotic activities."[77] The '845 reference includes data demonstrating the antithrombotic activity of a compound by measuring "platelet aggregation."[78] Based on the express teachings of the Fujisawa references, one of ordinary skill in the art would have understood the compounds disclosed therein to have significant COX-1 activity and would not have considered them to be promising candidates for COX-2 selective inhibitors.[79]

95. Third, the Merck '196 application prohibits attaching either of the phenyl rings to a heteroatom of the heterocycle. Following this teaching, none of the examples in either

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75 *See* ¶66, supra.

76 DeWitt, "Cox-2-Selective Inhibitors: The New Super Aspirins," *Molecular Pharmacology*, 1999, vol. 55, pp. 625-631; Meade, Smith and Dewitt, "The Differential Inhibition of Prostaglandin Endoperoxide Synthase (Cyclooxygenase) Isozymes by Aspirin and Other Non-Steroidal Anti-Inflammatory Drugs," *Journal of Biological Chemistry*, 1993, 268(9): 6610-6614 (PFC01603523-27).

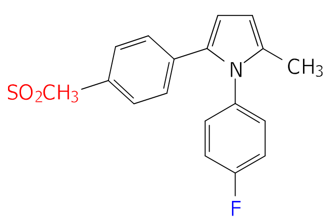
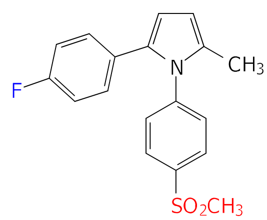
77 *See, e.g.*, '829 reference (DX-040), p. 3, ln 3, 22; p. 16, ln. 37; '845 reference (PFC01603002-72), p. 2, ln. 3, 22.

78 Fujisawa '845 reference, pp. 23-24 (PFC01603002-72).

79 *See, e.g.,* DeWitt, "Cox-2-Selective Inhibitors: The New Super Aspirins," *Molecular Pharmacology*, 1999, vol. 55, pp. 625-631; Meade, Smith and Dewitt, "The Differential Inhibition of Prostaglandin Endoperoxide Synthase (Cyclooxygenase) Isozymes by Aspirin and Other Non-Steroidal Anti-Inflammatory Drugs," *Journal of Biological Chemistry*, 1993, 268(9): 6610-6614 (PFC01603523-27).

Table I or Table II show either of the phenyl rings attached to a heteroatom. The Fujisawa references on the other hand, teach that one aryl ring must be bound to the heteroatom. Having relied on the Merck ’196 application to develop the Teva Pharmacophore, one of ordinary skill in the art would have interpreted the Fujisawa references as teaching away from using the pyrazole.

96. If, contrary to my opinion, one of ordinary skill in the art were motivated to try a pyrazole based on the Fujisawa references, the Fujisawa references teach a strong preference that the phenyl ring containing the methyl sulfone substituent should be attached to the 5-position of the pyrazole ring, not the nitrogen heteroatom at the 1-position of the pyrazole as is required by the patents-in-suit.[80] As demonstrated below, the position of the phenyl ring containing the methyl sulfone can have a significant effect on COX-2 activity.[81]

	
SC-57019[82]	**SC-56975[83]**
COX-1 IC50: >100µM	COX-1 IC50: >100µM

80 With respect to the ’829 Fujisawa reference (DX-040), 74 out of 79 examples have a sulfur containing substituent attached to the 5-position of the pyrazole (with 43 of those containing a methyl sulfone). Of the five examples that teach the sulfur-containing substituent attached to the 1-position of the pyrazole, only two contain a methyl sulfone. With respect to the ’845 (PFC01603002-72) Fujisawa reference, 218 of the 268 examples have a sulfur-containing substituent attached to the 5-position of the pyrazole (with 114 of those containing methyl sulfone). Of the six examples that have a sulfur-containing group attached to the 1-position of the pyrazole, only two contain a methyl sulfone.

81 *See also* Exhibit 3.

82 PFC00291120; PFC01592078; PFC01228796; PFC01552824.

83 PFC01592078; PFC01228721; PFC01552763.

COX-2 IC50: 0.511µM	COX-2 IC50: >100µM

Based on the teaching that the phenyl ring containing the methyl sulfone should be attached to a carbon atom (and, in particular, to the carbon at the 5-position), one of ordinary skill in the art would neither have been motivated to investigate compounds within claim 1 of the ’823 patent nor had any expectation that they would be COX-2 active.[84]

97. Fourth, Teva’s own reasoning precludes synthesizing pyrazoles. Teva’s experts state that one of ordinary skill in the art would have knowledge “about aspects of patent protection”[85] and, based on that knowledge, would have been motivated to synthesize compounds within the Teva Pharmacophore that contained heterocycles that were not disclosed in the Merck ’196 application. Based on Teva’s reasoning, it would be illogical for one of ordinary skill in the art to abandon the heterocycles in the Merck ’196 application due to patent concerns, only to synthesize pyrazole compounds that one of ordinary skill in the art would know are covered by the Fujisawa reference or, at best, obvious (based on Teva’s reasoning) in view of the Fujisawa references and in view of the claim that the Merck ’196 application teaches that methyl sulfone and sulfamyl were interchangeable.

XIV. THERE IS NO BASIS FOR TEVA’S TWELVE “OBVIOUS” COMPOUNDS

98. Combining the Merck ’196 application with the Fujisawa references would have resulted in significantly more than twelve compounds. Teva’s experts have made the following unfounded assumptions:

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[84] Although there is a single example in the ‘829 Fujisawa reference (DX-040) disclosing a compound where the methyl sulfone is attached to the phenyl at the 1-position of the heteroatom, all other examples including those for which data is provided teach the methyl sulfone substituent attached to the phenyl at the 5-position of the pyrazole ring.

[85] Cooperman Rep. ¶16; Baker Rep. ¶112; *see also* Trummlitz Rep. ¶32.

a. There was motivation to select the sulfamyl over the methyl sulfone.

b. The optional substituent on the heterocycles would be limited to a CN or CF_3.

c. The optional substituent on the phenyl "B" ring would be limited to four substituents.

d. The phenyl rings could be attached to the heteroatom.

e. The heterocycle is limited to the pyrazole.[86]

99. Combining the Merck '196 application with the Fujisawa references would have resulted in far more than twelve compounds. As discussed below, the assumptions on which Teva's experts come up with twelve "obvious" compounds are not supported by any teaching in the Merck '196 application, the Fujisawa references or otherwise:

A. There Is No Motivation to Select a Sulfamyl Over a Methyl Sulfone

(i) Decreasing Lipophilicity Does Not Guarantee Increased Oral Bioavailability

100. Teva's experts opine that one of ordinary skill in the art would choose a sulfamyl over a methyl sulfone because: (a) it was known that a "sulfamyl substituent would reduce lipophilicity"; (b) "the lipophilicity of a diphenyl heterocycle is very high"; and (c) "reducing lipophilicity would increase the bioavailability."[87]

101. This incorrectly assumes that one of ordinary skill in the art would have been concerned that those compounds containing the methyl sulfone within the Teva Pharmacophore had poor biolavailability. There is no teaching in the Merck '196 application or otherwise to that effect. In fact, Merck invested many millions of dollars developing rofecoxib,

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[86] For a discussion *see* XIII, *supra*.

[87] Baker Rep. ¶156.

a methyl sulfone disclosed in the Merck ’196 application, into a drug that made billions of dollars in the marketplace. Without a concern for bioavailability, there would have been no motivation to select substituents on that basis. Furthermore, even if there were a concern about bioavailability, there would have been no motivation to pick the sulfamyl to improve bioavailability rather than to make another change at some other position of the molecule in order to improve bioavailability, *e.g.*, by adding an appropriate substituent on the heterocycle or other phenyl ring or by changing a phenyl ring to a heterocycle.

102. Moreover, even if there were a motivation to improve bioavailability and to pursue this end by changing a methyl sulfone to a sulfamyl substituent, there is no reasonable expectation that this change would improve the compound’s bioavailability; in fact, as explained below, one of ordinary skill in the art could have concluded that the change could lead to poorer bioavailability.

103. Oral bioavailability depends heavily upon three components: solubility (the ability of the compound to dissolve from the crystalline state into solution), permeability (the ability of the compound to pass through the gastrointestinal tract and/or cell walls) and metabolism (the body’s ability to breakdown the compound). Oral bioavailability is normally enhanced by improved solubility and permeability and reduced by increased metabolism, all else being constant. More lipophilic compounds tend to exhibit poorer solubility, but increased permeability. Thus, increasing lipophilicity or solubility, all else being equal, will likely increase a compound’s oral bioavailability. However, decreasing lipophilicity generally increases solubility, but decreases permeability, so the net outcome on bioavailability can be unclear.

104. Prediction of cell permeability is relatively straightforward except when active transport is involved (some molecules are actively transported into cells by cell membrane

components and some are effluxed from cells by protein pumps). Prediction of solubility is complicated. Prediction of bioavailability is even less certain, owing to the solubility/permeability competition and the influence of metabolism. For the permeability component, changing from a methyl sulfone to a sulfamyl group should reduce lipophilicity and reduce bioavailability. For solubility, the outcome of a methyl sulfone to sulfamyl change in the present case is unclear. The methyl sulfone analog of celecoxib has no hydrogen-bond donating groups, so there can be no hydrogen bonding to stabilize the crystal. However, upon changing to the sulfamyl analog, there are now both hydrogen-bond donating (NH_2) and accepting (SO_2) sites, so hydrogen bonding is then expected in the crystal. Hydrogen bonding in the crystal stabilizes it, raises its melting point and may well lead to reduced solubility and bioavailability. Thus, even if one expected poor solubility for a methyl sulfone-containing compound, it is not clear that a change from a methyl sulfone to a sulfamyl would improve either solubility or bioavailability.

(ii) Sulfa Allergies Were Well Known in the Art

105. Further, one of ordinary skill in the art would have avoided the methyl sulfone to sulfamyl replacement because it was well known in the art that sulfamyl-containing "sulfonamide drugs" are associated with a sulfa allergy that manifests itself as a severe skin reaction.[88] Thus, the well-known motivation to avoid drugs with potential to trigger allergic reactions would have taught away from the sulfamyl.

(iii) DuP-697 and the Fujisawa References Teach Away from the Sulfamyl

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88 *See e.g.*, Reider, "Diagnosis of sulfonamide hypersensitivity reactions by in-vitro 'rechallenge' with hydroxylamine metabolites," *Ann. Intern. Med.*, 1989, 110: 286-289 (PFC01606456-60); Knowles, "Should Celecoxib Be Contraindicated in Patients Who Are Allergic to Sulfonamides?", *Drug Safety*, 2001, 24(4): 239-247; Celebrex® Product Insert (PFC01603247-55).

106. Based on Teva's logic that the methyl sulfone is interchangeable with the sulfamyl, the prior art DuP-697 compound and the Fujisawa references would have taught a preference for the methyl sulfone.

B. There is No Teaching to Limit the Optional Substituent on the Heterocycle to CF_3 or CN

(i) The Examples of the Merck '196 Application and the Fujisawa References Teach Numerous Potential "Optional" Heterocycle Substituents

107. Teva's experts opine that one of ordinary skill in the art would be motivated to use only the CF_3 or CN substituents based on the teachings of the Fujisawa references. I disagree for the following reasons.

108. First, there would have been no motivation to rely on the substituents taught by the Fujisawa references as opposed to those taught by the Merck '196 application, nor would there have been an expectation that the compounds would have COX-2 activity. Such a position is inconsistent with the opinion of Teva's experts that one of ordinary skill in the art "would have stayed close to the pharmacophore taught in the Merck '196 application."[89] Based on this reasoning (which is Teva's, not mine), one of ordinary skill in the art would have first looked to the Merck '196 application for potential substituents. As demonstrated in the table below, the examples of Merck '196 application teach seven different possible "optional" substituents and do not teach the CN substituent.[90]

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89 Cooperman Rep. ¶ 91.

90 To the extent that Teva's experts are arguing that one of ordinary skill in the art would have looked to the Fujisawa references because those patents cover pyrazoles, this is inconsistent with their position that one would have understood that heterocycles were interchangeable.

109. Second, there is no teaching in the Fujisawa references to choose only the CF_3 or CN substituents. The ’829 reference teaches compounds containing eight possible substituents (the number of examples on which they appear are in parentheses): trifluoromethyl ($-CF_3$) (30); difluoromethyl (CF_2H) (26); ester (9); carboxamide (5); carbonitrile (-CN) (5); bromo (-Br) (3); chloromethyl ($-CH_2Cl$) (2); and carboxylic acid ($-CO_2H$) (1). One of ordinary skill in the art would not choose substituents based on the number of examples in which they appear, and even if they did, there are alternative substituents which are as prevalent as the CF_3 or CN options. Similarly, the ’845 reference teaches that the heterocycles can be unsubstituted or contain one of more than 20 possible substituents in all:

“Optional” Heterocycle Substituents Taught In the Examples of Teva’s References

Merck ’196 Application	Fujisawa ’829 reference	Fujisawa ’845 reference

hydroxyisopropyl (-$C(CH_3)_2OH$) isopropyl (-$CH(CH_3)_2$) carboxylic acid (-CO_2H) methyl (-CH_3) *gem*-dimethyl (-$(CH_3)_2$) trifluoromethyl (-CF_3)	trifluoromethyl (-CF_3) difluoromethyl (-CF_2H) esters carboxamide carbonitrile (-CN) bromo (-Br) chloromethyl (-CH_2Cl) carboxylic acid (-CO_2H)	esters carboxylic acid (-CO_2H) carboxamide pyrrolidinylcarbonyl 4-methyl-1-piperazinylcarbonyl pyrazolylcarbonyl carbonitrile carbonitrile hydrochloride N,N-dimethylaminomethyl trifluoromethyl (-CF_3) acetyl methoxyacetyl fluoromethyl difluoromethyl (-CF_2H) hydrido (-H) fluorophenyl pyrazolylmethyl acetate bromo (-Br) carbonyl chloride N- pyrazolyl acetamide N- pyrazolyl carbamate N- pyrazolyl methanesulfonamide pyrazolylmethylamine chloromethyl (-CH_2Cl) methylsulfonyl 5-tetrazolyl methylthio (-SMe) methylamine

110. Thus, even if one were to rely solely on the Merck ’196 application and the Fujisawa references, and then only relied on the examples in those references, the list of possible substituents would be significantly longer than the two suggested by Merck’s experts. If one were to consider all of the “optional” heterocycle substituents taught by the genus of each of the Merck ’196 application and the Fujisawa references, the list would be longer still.

111. Teva’s experts ignore that the Merck ’196 application does not specify the location of the “optional” heterocycle substituent, and the Fujisawa references teach that the optional substituent can appear on either the 3- or 4- position of the pyrazole. Thus, there is no

motivation in the Merck ’196 application or Fujisawa references to limit the position of the optional substituent on the heterocycle to the 3-position as Teva’s experts suggest.

112. Furthermore, if (based on the reasoning of Teva’s experts) one of ordinary skill in the art would have been motivated to combine the compounds in the Merck ’196 application with other anti-inflammatory patents, then one of ordinary skill in the art would also have looked at all diphenyl anti-inflammatory references to generate a complete list of possible substituents. There is no basis to only selectively combine the references as Teva’s experts have done or to limit the references to the Merck ’196 application and the Fujisawa references, while ignoring the teaching of other diphenyl heterocycle patents.

(ii) Adding a CF_3 Substituent Does Not Alter the Electron Configuration of a Pyrazole

113. Dr. Cooperman states that one of ordinary skill in the art “would have been motivated to select a pyrazole having a CF_3 substituent at the 3-position . . . because this structure is similar in electronic structure to the thiophene and pyrrole of the Merck ’196 application.”[91] Dr. Cooperman states that the pyrrole and thiophene rings have six shared electrons and the pyrazole ring has seven shared electrons.[92] Thus, Dr. Cooperman concludes, one of ordinary skill in the art would have chosen a CF_3 substituent, which is a good electron withdrawing group, to reduce the “shared electron density of the pyrazole ring.”[93]

Dr. Cooperman’s analysis demonstrates a remarkable error in knowledge of basic organic chemistry, and it reveals how contrived the efforts of Teva’s experts became in trying to invent a

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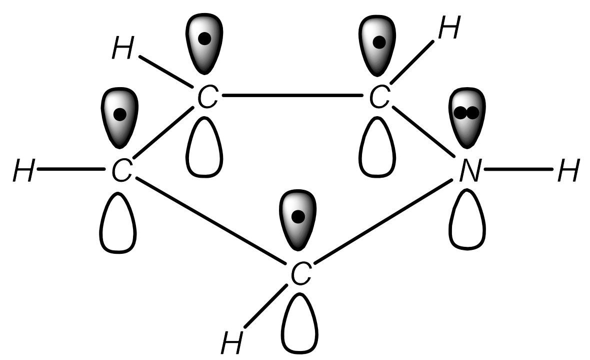
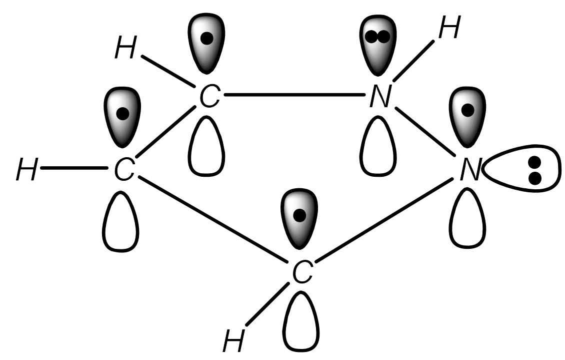
91 Cooperman Rep. ¶108.

92 Cooperman Rep. ¶¶109-110.

93 Cooperman Rep. ¶110.

motivation to restrict the substituents and to come up with the absurd notion of the "twelve immediately obvious compounds."[94]

114. In any elementary course in organic chemistry, students learn that a furan, thiophene, pyrrole, imidazole and pyrazole are all examples of aromatic heterocycles that are characterized by having six shared pi electrons (isoelectronic with the pi system of benzene); the correct electron assignments are shown below for pyrrole and pyrazole.[95]. Therefore, there is no basis to select a pyrazole over these other electronically similar heterocycles.

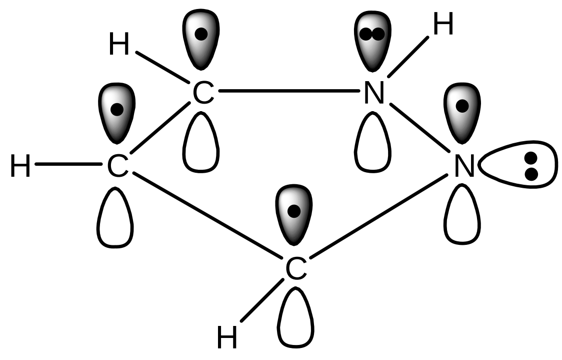
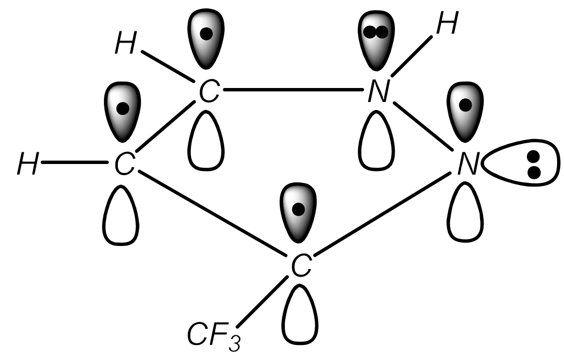
	
Pyrrole	**Pyrazole**

115. The CF_3 substituent is irrelevant to the pi electron count, as illustrated by the diagram below. So, by Dr. Cooperman's mistaken logic, since the CF_3 group "reduces the shared electron density of the pyrazole ring"[96], then a trifluoromethylpyrazole would not be similar in electronic structure to a thiophene or pyrrole, and one of ordinary skill in the art would presumably not pursue trifluoromethylpyrazoles.

94 Cooperman Rep. ¶121.

95 *See, e.g.,* Loudon, "Organic Chemistry," Second Edition, 1988, p.622-623 (PFC01603492-94).

96 Cooperman Rep. ¶110.

	
Pyrazole Without CF_3	**Pyrazole With CF_3**

(iii) Adding a CF_3 Substituent Would Increase Lipophilicity

116. The suggestion that one of ordinary skill in the art would chose a CF_3 substituent is inconsistent with the reasoning Teva's experts use to justify choosing the sulfamyl substituent: its ability to reduce lipophilicity. As discussed above, Teva's experts state that one of ordinary skill in the art would choose a sulfamyl (over a methyl sulfone) in order to reduce the lipophilicity (and increase the bioavailability) of the diphenyl heterocycles, which were known in the art to be very lipophilic. This reasoning by Teva's experts, if correct, would have taught one of ordinary skill in the art away from using a CF_3 substituent because it is well known that CF_3 substituents are very lipophilic. For example, the octanol/water partition coefficients (log $P_{o/w}$) are known to be 2.13, 2.73 and 3.01 for benzene, toluene, and trifluoromethylbenzene, respectively.[97]

[97] Hansch et al, "Exploring QSAR-Hydrophobic, Electronic, and Steric Constants," *Am. Chem. Society*, Washington, DC, 1995.

(iv) Canadian Patent 1,130,808 Does Not Teach Using a CF_3 substituent with the Teva Pharmacophore

117. As an initial matter, Teva's experts admit that the '808 patent does not teach "the sulfamyl or methylsulfonyl substituent,"[98] the very substituents Teva's experts state are "critical" for COX-2 activity and selectivity.[99] Moreover, the '808 patent to teach that the compounds are COX-2 selective.

118. I also disagree that the '808 patent teaches "all of the [other] features of the pharmacophore of the Merck '196 application."[100] As set forth in the statement below, the inventors of the '808 patent were uncertain whether they had created 1,5-diphenyl pyrazoles (formula 1, wherein the rings are adjacent) or 3,5-diphenyl pyrazoles (formula 2, wherein the rings are not adjacent):

> The exact proportions of the isomers of formulae 1 and 2 which are obtained in this manner are not known, and it may well be that predominantly only the isomer of formula 1 is obtained in a given reaction, while predominantly only the isomer of formula 2 is obtained in another, and mixtures of varying proportions of isomers of formulae 1 and 2 are obtained in still another case. However, it should be noted that all the compounds prepared in this manner are characterized by their respective nmr spectra which confirm the presence of CF_3 and of the substituents R_1 and Ar on the pyrazole ring, but that nmr is not capable of distinguishing between any pair of isomeric compounds of formulae <u>1</u> and <u>2</u>, although chromatography may permit separation of the two isomers.[101]

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98 Baker Rep. ¶198.

99 Baker Rep. ¶144.

100 Baker Rep. ¶198.

101 '808 patent, page 3, lines 11-23. *See also* Example 1, page 8; Example 2, p. 8-9 (DX-037).

Since the Teva Pharmacophore requires that the phenyl rings be adjacent, it would have been unclear to one of ordinary skill in the art that the compounds disclosed possessed this required phenyl ring orientation. Such uncertainty would have taught away from relying on the ’808 patent.

119. Thus, having failed to teach (a) the “required” methyl sulfone or sulfonamide, (b) adjacent phenyl rings and (c) COX-2 activity or selectivity, one of ordinary skill in the art seeking to make a COX-2 selective compound would not have been motivated to make the compounds in the ’808 patent, and would certainly not have had an expectation that using a single substituent would confer COX-2 selectivity or activity on compounds within the Teva Pharmacophore.[102]

C. There is No Teaching that the “Optional” Substituent on the Phenyl “B” Ring Should Be Limited to Four Substituents

(i) The Merck ’196 Application and Fujisawa References Teach Numerous “Optional” Phenyl “B” Substituents

120. First, as stated above with respect to the “optional” heterocycle substituents, assuming the reasoning of Teva’s experts that one of ordinary skill in the art “would have stayed close to the pharmacophore taught in the Merck ’196 application,”[103] they would have at a minimum looked to the examples of the Merck ’196 application for potential substituents.[104] As demonstrated in the table below, the examples of the Merck ’196 application

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[102] Moreover, if one of ordinary skill in the art were to rely on the ’808 patent simply because it teaches a diphenyl heterocycle that is anti-inflammatory, then there are numerous other patents that one could have turned to in order to find possible substituents. There was no motivation to choose the ’808 over any other patent (DX-037).

[103] Cooperman Rep. ¶ 91.

[104] Once again, even if one were motivated to make compounds within the Teva

(continued...)

teach that the phenyl "B" ring can be optionally substituted with up to two[105] of eight different substituents. Although fluoro appears in the most examples, there is no teaching in the Merck '196 application to only synthesize compounds with a fluoro substituent.

121. Similarly, there was no teaching in the Fujisawa references to choose only the fluorine, methyl, methoxy and nitro substituents. The examples of the Fujisawa references teach dozens of potential optional substituents.

"Optional" Phenyl "B" Substituents Taught In the Examples of Teva's References

Merck '196 Application	Fujisawa '829 reference	Fujisawa '845 reference
hydrogen (-H) fluoro (-F) chloro (-Cl) bromo (-Br) methoxy (-OMe) carboxylic acid ($-CO_2H$) acetic acid ($-CH_2CO_2H$) hydroxyisopropyl ($-C(CH_3)_2OH$) 2-propionic acid ($-CH(CH_3)CO_2H$)	Methoxy Methylthio Methylsulfinyl Cyano Carboxy Phenoxy Carbamoyl Acetyl Ethoxycarbonyl Hydroxymethyl Hydroxy Methoxy-methoxy Ethoxy Isopropoxy Nitro Hydrogen Methylenedioxy	Fluoro Methylthio Tert-butyl Hydroxy Methoxy Nitro N-formyl-methylamino Methyl Acetyl Chloro Acetamido Cyano Methylamino Methylsulfonyl-oxy Amino Dimethylamino Methylsulfinyl Ethylamino Methylsulfonyl-amino Formylamino

If one were to consider all of the "optional" heterocycle substituents taught by the genus of the Merck '196 application and the Fujisawa references, the list would be much longer.

104 (...continued)
Pharmacophore that had optional phenyl "B" substituents from the Fujisawa references, there would be no expectation that those compounds would have COX-2 activity or selectivity.

105 Teva's selection of 12 "obvious" compounds ignores this teaching, which is also found in the Fujisawa references.

122. Additionally, Teva's experts ignore other teachings of the Fujisawa references in order to artificially limit the number of compounds. The Fujisawa references also teach that (a) there can be up to two substituents on the phenyl "B" ring and (b) the substituent can be attached to the 2-, 3-, or 4- position of the heterocycles. This encompasses a large number of possibilities.

(ii) The Optional Substituent's Effect on Cox-2 Activity was Unknown

123. Contrary to the assertions of Drs. Cooperman and Baker, the Merck '196 application and the Fujisawa references do not teach that the "optional" substituents "on phenyl 'B' are unimportant in the binding of the inhibitors to the enzyme active site."[106] As explained above, there is no basis to make this conclusion. The references do not state such a conclusion, nor do they contain the extensive SAR data required to support such a conclusion. Further, based on the understanding that small changes can have significant effects on activity, one of ordinary skill in the art would not have expected all optional substituents to have similar activity.

(iii) There Was No Motivation to Replace the Fluorine Substituent

124. Teva's experts opine that one of ordinary skill in the art would have replaced the fluorine substituent with a methyl or methoxy group in an effort to reduce half-life.[107] No basis for doing so is disclosed in the Merck '196 application, the Fujisawa references or elsewhere. In 1993 it was impossible to predict the half-life of a compound without making and testing it. The same is true today. Absent a suggestion in the Merck '196 application or the

[106] Cooperman Rep. ¶¶88-89; Baker Rep. ¶164.

[107] Trummlitz Rep. ¶¶88-91; Baker Rep. ¶¶165-166; Cooperman Rep. ¶¶119-120.

Fujisawa references that the compounds have a long half-life, one of ordinary skill in the art would not have been motivated to reduce half-life.[108]

125. Moreover, even if there were a motivation to reduce half-life of the compounds within the Teva Pharmacophore, there was no motivation to do so by changing the substituent at the phenyl "B" position as opposed to any other substituent. There are numerous ways that one could have tried to reduce the half-life. For example, one of ordinary skill in the art could very well have left the fluoro and attached a methyl group to the heterocycle to incorporate an alternative site of potential metabolism.

126. Finally, even if one of ordinary skill in the art would have been motivated to reduce the half-life of the compounds within the Teva Pharmacophore by installing a more easily metabolizable group in place of the fluorine, there would have been no expectation that making compounds within the Teva Pharmacophore with a methyl or methoxy attached to the phenyl "B" position would result in a compound with a desirable half-life. Such a substitution may just as plausibly have resulted in a compound that had a half-life that was so short as to make the compound unusable.[109]

(iv) Nitro Did Not Have to be Avoided

127. I do not believe that one of ordinary skill in the art would have excluded the nitro (-NO_2) substituent at the early stages of drug discovery based on the fact that, in some

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[108] This suggestion demonstrates the hindsight used by Teva's experts to obtain the Teva Pharmacophore, and appears to be based on plaintiffs' experience with SC-58125, a compound containing a fluoro substituent. Although SC-58125 exhibited good COX-2 activity and selectivity, it was nevertheless abandoned because of a long half-life. *See* Galbraith Rep. ¶¶33-42.

[109] Trummlitz Rep. ¶90.

cases, it "may lead to unwanted toxicity."[110] Numerous commercial drugs, used to treat a variety of medical conditions, contain nitro groups. For example, nitro-containing compounds are sold as at least calcium channel blockers[111], H_2 receptor antagonists[112], muscle relaxants[113], anti-cancer drugs[114], and anti-protazoals[115].

D. The Merck '196 Application Teaches Away from Attaching a Phenyl to N1 of the Pyrazole

128. As explained above, the genus of the Merck '196 application prohibits bonding the phenyl ring to the heteroatom of the heterocyclic ring. Based on this teaching, one of ordinary skill in the art would not have been motivated to attach the phenyl ring to the nitrogen in the 1-position of the pyrazole ring and would not have had any expectation that such an attachment would result in COX-2 selective compounds.

129. Ignoring this express teaching in the Merck '196 application, Teva's experts nevertheless opine that the Fujisawa references teach a phenyl group attached to the heteroatom of the pyrazole. Teva's experts, however, fail to suggest any motivation to choose the teaching of the Fujisawa references over those of the Merck '196 application. Doing so is

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110 Trummlitz Rep. ¶87; Baker Rep. ¶163; Cooperman Rep. ¶116.

111 *E.g.*, Nimotop® (nimotidine), 2006 Physician's Desk Reference ("PDR"), p.774; Cardene® (nicardipine hydrochloride), 2006 PDR, p.1129; Sular® (nisoldipine), 2006 PDR, p.1163; Adalat® (nifedipine), 2006 PDR, p.2978 (PFC01606288-315).

112 *E.g.*, Zantac® (ranitidine hydrochloride), 2006 PDR, p.1597 (PFC01606288-315).

113 *E.g.*, Dantrium® (dantrolene sodium), 2006 PDR, p.2691 (PFC01606288-315).

114 *E.g.*, Eulexin® (flutamide), 2006 PDR, p.3023 (PFC01606288-315).

115 *E.g.*, Alinia® (nitazoxanide), 2006 PDR, p.2840; Tindamax® (tinidazole), 2006 PDR, p.2670 (PFC01606288-315).

inconsistent with their statement that one of ordinary skill in the art "would have stayed close to the pharmacophore taught in the Merck '196 application."[116]

130. Finally, if, as Teva's experts suggest, one of ordinary skill in the art would have relied on the Fujisawa references for the positions of the phenyl rings, then one of ordinary skill in the art would not have been motivated to synthesize compounds wherein the phenyl ring bearing the sulfamyl or methyl sulfone was attached to the nitrogen heteroatom at the 1-position of the pyrazole. As discussed above, examples in the Fujisawa references teach attaching the sulfur-containing substituent (and in particular the methyl sulfone) to the phenyl ring at the 5-position of the pyrazole.[117] Thus, one of ordinary skill in the art would have understood the Fujisawa references to teach away from celecoxib and the genus of the '196 patent which requires the sulfamyl phenyl to be attached to the nitrogen at the 1-position of the pyrazole.

XV. THE REFERENCES CITED BY TEVA ARE NO MORE RELEVANT THAN THE REFERENCES THAT WERE BEFORE THE PATENT EXAMINER

131. The specification of the '823 patent sets forth numerous prior art references and structures which teach "[t]he use of 4-[3,4,5-trisubstituted-pyrazol-l-yl]benzene sulfonamides."[118] The specification states that Feid-Allah[119] teaches the compound (1) set forth below. The genus of claim 1 of the '823 patent includes compound (2) set forth below. The compound of the '823 patent (2) differs from the Feid-Allah compound (1) by only a single atom. Specifically, the Feid-Allah compound (1) has a methyl ($-CH_3$) whereas the compound of the '823 patent (2) has a fluoromethyl ($-CH_2F$) at the 3-position.

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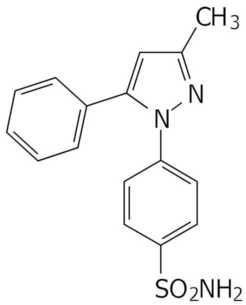
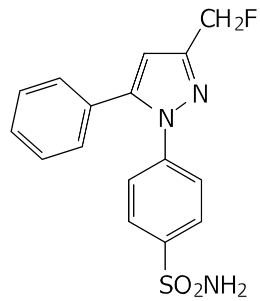
116 Cooperman Rep. ¶91.

117 *See* footnote 80, *supra*.

118 '823 patent, col. 1, lns. 54-67 (DX-012).

119 *Pharmazie*, 36, 754 (1981) (DX-280).

	
(1) **Feid-Allah Compound**	**(2)** **Compound Within Claim 1 of the ’823 Patent**

132. I understand that Teva alleges in its Interrogatory Responses that the patents-in-suit are obvious in light of a number of patent and literature references.[120] Since the Feid-Allah compound (1) differs from the compound of the ‘823 patent (2) by a single atom, there is no compound that can be closer to the genus of the ‘823 patent. For this reason and the reasons listed below, it is my opinion that none of the references cited by Teva are more relevant than the Feid-Allah reference and are at most cumulative.

A. References that Do Not Disclose Pyrazoles

133. Teva cites the following references that do not teach pyrazoles as required by the patent-in-suit. As stated in detail above, due to the known and expected differences between heterocycles, the following references are less relevant than the Feid-Allah reference.

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[120] *See* Teva’s Response to Pfizer’s First Set of Interrogatories, Response to Interrogatory No. 3; Teva’s Second Supplemental Response to Pfizer’s First Set of Interrogatories, Supplemental Response to Interrogatory No. 3. I understand that Teva’s experts are not relying on the majority of these references. Although I briefly discuss them herein, I reserve my right to address them in greater detail if Teva attempts to rely on them at trial.

(i) The Merck '196 Application

134. As set forth in great detail above, the Merck '196 application discloses a broad genus of compounds that include diaryl heterocycle compounds that can be substituted with a methyl sulfone or sulfamyl. The Merck '196 application does not teach pyrazole compounds. For this and the numerous reasons listed above, the Merck '196 application is no more relevant than the Feid-Allah reference.

(ii) The DuP-697 References[121]

135. The DuP-697 references disclose DuP-697, a 2,3-diphenyl thiophene wherein the 2-position phenyl is substituted with a fluorine, the 3-position phenyl is substituted with a methyl sulfone, and the thiophene is substituted with a bromine at the 5-position. The DuP-697 references do not teach pyrazole compounds or the sulfamyl group. With respect to celecoxib, the DuP-697 references do not teach the pyrazole, the trifluoromethyl heterocycle substituent at the 3-position and the 5-position phenyl substituted with a methyl group.

(iii) U.S. Patent 3,427,305 (the "'305 patent")

136. The '305 patent is directed to a genus of diphenyl pyrrole compounds that may "reduce edema and granuloma-formation associated with the inflammatory response to tissue insult."[122] The genus of compounds is defined as follows: (a) a sulfamyl phenyl attached at the 1-position of the pyrrole; (2) carboxyalkyl group attached to the 2-position of the pyrrole; and (3) a phenyl substituted by a halogen at the 5-position of the pyrrole ring. Because the '305

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121 Gans *et. al*., "Anti-Inflammatory and Safety Profile of Dup 697, a Novel Orally Effective Prostaglandin Synthesis Inhibitor," 254 *J. Pharm. and Exp. Ther.* 180 (1990) (PX-031), and/or slides entitled "DuP-697 as an Agent Which May Be a Selective Cyclooxygenase Inhibitor" presented by William Galbraith at the Keystone Prostaglandin Conference on January 11, 1992 (collectively "the DuP-697 references")

122 '305 patent, col. 1, lns 55-59 (DX-160).

patent neither discloses pyrazoles nor teaches combining the sulfamyl with a pyrazole, the ’305 patent is no more relevant than the Feid-Allah reference.

137. With respect to celecoxib, the ’305 patent also does not teach: (a) the pyrazole; (b) the phenyl at the 5-position substituted with a methyl group; or (c) the trifluoromethyl substituent at the 3-position of the pyrazole.

B. References that Disclose Diaryl Pyrazoles

138. Teva cites the following references which disclose pyrazole compounds but do not disclose the sulfamyl or methyl sulfone substituent. For the reasons stated below, it is my opinion that these references are no more relevant than the Feid-Allah reference.

(i) U.S. Patent 4,146,721 (the “’721 patent”)

139. The ’721 patent teaches a genus of pyrazole compounds which includes diphenyl pyrazoles, non-phenyl pyrazoles and triphenyl pyrazoles (containing a phenyl ring at the 3-position of the pyrazole which is prohibited by each of the patents-in-suit). The ’721 patent does not teach diphenyl pyrazoles containing a methyl sulfone or sulfamyl substituent or a preference for any of the other substituents that may be attached to the phenyl ring at the 1-position of the pyrazole as set forth in the patent-in-suit. Thus, it is my opinion that the ’721 reference is no closer than the Feid-Allah reference.

140. With respect to celecoxib, the ’721 patent does not teach: (a) the phenyl substituted with a methyl group or (b) the trifluoromethyl substituent.

(ii) CA 1 130 808 (the “’808 patent”)

141. As discussed above, the ’808 patent does not disclose a sulfamyl substituent and, for this reason and all of the other reasons cited herein, the ’808 patent is no more relevant than the Feid-Allah reference.

(iii) Makki[123]

142. Makki discloses 1,3,5-triphenyl pyrazoles. The patents-in-suit preclude attaching an aryl group to the 3-position of the pyrazole. Furthermore, Makki does not disclose the sulfamyl substituent. For these reasons, Makki is no more relevant than the Feid-Allah reference.

C. References that Disclose Diaryl Pyrazoles and a Methyl Sulfone Substituent

143. The following references cited by Teva disclose a pyrazole compound and a methyl sulfone substituent on a phenyl ring attached to the pyrazole. As discussed above, since there was no teaching that a methyl sulfone and sulfamyl are interchangeable, and these references do not disclose the sulfamyl group, it is my opinion that the references are no more pertinent than, and are at best cumulative of, the Feid-Allah reference that discloses both the pyrazole and the sulfamyl substituent.

(i) The Disclosed U.S. 5,134,142 (the "'142 patent")

144. The '142 patent , which was before the patent examiner[124], discloses a genus of 1,5-diaryl pyrazole compounds that can be optionally substituted with a trifluoromethyl or other substituent and wherein the aryl rings: (a) can be phenyl; (b) can be attached to the heteroatom; (c) must be adjacent; and (d) can be substituted with a methyl sulfone substituent, among other groups, at the para-position of one either phenyl rings. However, the examples of the '142 patent teach a preference for attaching the methyl sulfone to the phenyl at the 5-position of the heterocycle.

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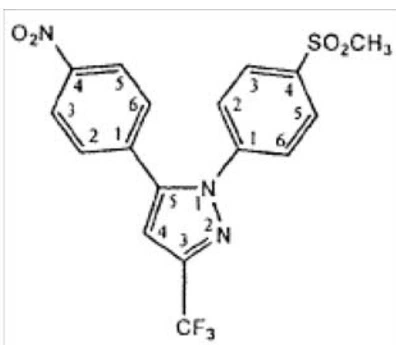
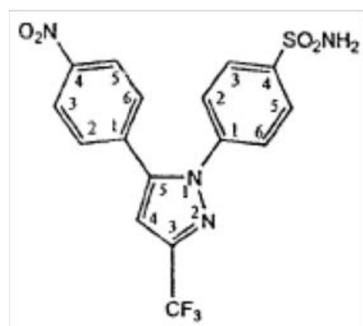
123 Makki *et al.*, "Pyrazole derivatives. Part I. Synthesis and Spectra of Trisubstituted Pyrazoline and Pyrazole Derivatives With Possible Hypoglycemic Activity," Heterocycles, vol. 121: 134017m (1994) (PFC01561149-50).

124 '823 patent, col. 1, lns. 38-32 (DX-012).

(ii) The Fujisawa References

145. The Fujisawa references teach a similar genus and, as discussed above, demonstrate through the examples a preference for attaching the methyl sulfone to the phenyl ring at the 5-position of the pyrazole. As an initial matter, the Fujisawa references do not teach the sulfamyl substituent and are therefore no more relevant than the Feid-Allah reference.

146. I understand that Mr. Smith states that the ’829 Fujisawa reference is not cumulative of the ’142 patent and the other references before the patent examiner because of a single example, example 23-3 (3), that is closer to a nitro containing compound of claim 11 (4) than any other compound in the ’142 patent.[125]

	
(3) **’829 Patent, Example 29-3**	**(4)** **’823 Patent, Claim 11**

147. While I agree that Example 29-3 (3) is closer to the nitro compound of claim 11 (4) than any compound in claim 11 of the ’823 patent, compounds (3) and (4) are less close in structure than compounds (1) and (2), above.[126] A -H to -F change is less significant than a $-CH_3$ to $-NH_2$ change in view of the substantial alteration of hydrogen bonding potential

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[125] Smith Rep. ¶163.

[126] *See* ¶¶131-132, *supra*.

and acidity associated with the latter change. Therefore, at best, the ’829 Fujisawa reference is no more relevant than the Feid-Allah reference.

(iii) U.S. Patent 5,051,518 (the “’518 patent”)

148. The ’518 patent discloses a genus containing millions of compounds including 1,5- diphenyl compounds wherein a possible substitution pattern could result in a methyl sulfone being attached to the phenyl at the 1-position of the pyrazole. There is no teaching to choose the methyl sulfone substituent to the exclusion of the numerous other substituents listed, and in fact the ’518 patent teaches a preference for lower alkoxy, halo, hydrogen, trifluoromethyl, and lower alkyl substituents.[127] The ’518 patent does not teach diphenyl pyrazoles containing a sulfamyl substituent as set forth in the patents-in-suit. Thus, the ’518 patent is at best cumulative of the Feid-Allah reference.

149. With respect to celecoxib, the ’518 patent does not teach the trifluoromethyl substituent. Furthermore, though the ’518 patent teaches that a phenyl can be substituted with a methyl, it does not teach choosing the methyl over the other the hundreds of other substituents that are claimed.

D. References that Disclose Diaryl Pyrazoles and a Sulfamyl Substituent

150. Finally, Teva cites several reference that disclose diaryl pyrazoles wherein one aryl ring can be substituted with a sulfamyl substituent. For the reasons stated below, these references are at best cumulative of the Feid-Allah reference.

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127 ’518 patent, col. 4, lns. 47-51 (PFC01604055-75).

(i) El-Khawass[128]

151. The aim of the authors was to "synthesize compounds containing two pyrazole moieties directly attached to each other," with the hope that the compounds would be "a potent antipyretic, analgesic or anti-inflammatory agent."[129] The article describes a 1,3-diphenyl pyrazole that is formed as an intermediate in the reaction, and teaches that the phenyl ring at the 1-position can be substituted with a sulfamyl. Since the phenyl rings are not adjacent, El-Khawass is lacking an limitation of the patents-in-suit. Furthermore, the patents-in-suit prohibit attaching a phenyl ring to the 3-position of the pyrazole. Thus, this reference is no more relevant than the Feid-Allah reference.

(ii) Mokhtar I[130]

152. Mokhtar I discloses two diaryl pyrazole structures (11 and 12) and describes a substitution pattern that teaches attaching a sulfamyl to the phenyl at the 1-position of the pyrazole. Both of these structures can be substituted, but require a methyl group at the 3-position. The sulfamyl-containing compounds of structures 11 and 12 (set forth in Tables 10 and 11) are outside of the genus (in the specification and the claims) of the '823 and '165 patents. The compounds would fall within the genus in the specification of the '068 patent, but not the genus of claim 1. The sulfamyl containing compound of structure 12 is excluded by a proviso of claim 1 ("R^4 is not 4-chlorophenyl when R^2 is methyl and R^3 is bromo"). These compounds are

128 El-Khawass et al., "The Difference in the Behaviour of Hydrazine and p-Substituted Phenylhydrazines on Various 4-(3-Aryl-3-Oxopropenyl) Antipyrines," Journal of Chinese Chemical Society, vol. 37, pp. 605-609 (1990) (PFC01602829-33).

129 *Id.*, pp. 605-606.

130 Mokhtar, "Synthesis of Nitrogeneous Compounds from δ-Unsaturated 1,3-Dicarbonyl Esters. Part I. Substituted Pyrazoles, Isooxazoles and Oxyquinoxalines," J. Chem. Soc. Pak., vol. 10, no. 4, pp. 414-424 (1988) ("Mokhtar I") (DX-043)

no closer to the genus of the patents in suit than the Feid-Allah compound (1). Accordingly, Mokhtar I is at best cumulative of the Feid-Allah reference.

(iii) Mokhtar II[131]

153. Mokhtar II discloses two groups of diaryl pyrazoles represented by structure 4 and structures 7, 8 and 10. First, with respect to structure 4, the compounds depicted do not disclose a sulfamyl and each compound has a methyl in the 3-position of the pyrazole, which, for the reasons stated above with respect to Mokhtar I, is not within the claims of the patents-in-suit. Second, the examples of structure 4 contain a nitro-group attached to the phenyl at the 1-position of the pyrazole, which is not within the genus for any of the patents-in-suit. Third, compound 4 is excluded from the genus (in the specification and claims) of the ’068 patent by a proviso of claim 1 (“R^4 is not aralkenyl when R_2 is carboxyl”).

154. Each of the structures within the second group (structures 7,8 and 10) contain a spacer group at the 5-position of the pyrazole which prevents the phenyl ring from attaching directly to the heterocycle. This is prohibited by the genus of the ’823 and ’165 patents. Although such a spacer is covered by the genus in the specification of the ’068 patent, it is excluded from the genus of claim 1 of the ’068 patent by a proviso (“R^4 is not aralkenyl when R_2 is carboxyl, aminocarbonyl or ethoxycarbonyl”). For these reasons, Mokhtar II is no more relevant than the Feid-Allah reference.

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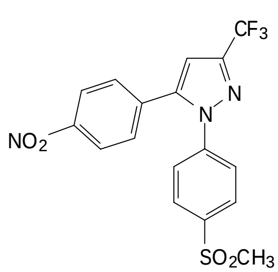
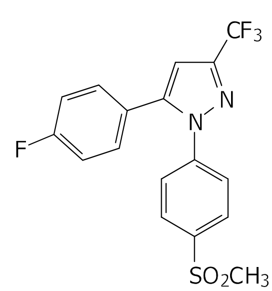
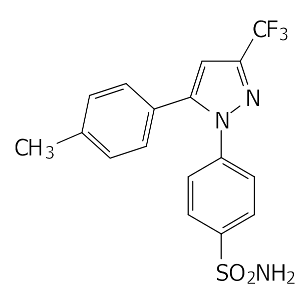
131 Mokhtar, “Synthesis of Nitrogenous Compounds. Part II,” Pak. J. Sci. Ind. Res. vol. 33, nos. 1-2, pp. 30-36 (Jan-Feb. 1990) (“Mokhtar II”) (DX-042).

(iv) Solomon[132]

155. Soliman is directed to pyrazole compounds having a phenyl ring containing a sulfonylurea attached at the 1-position of the pyrazole and a phenyl ring indirectly attached to the 5-position of the pyrazole. As a result of the requirement that these compounds have a sulfonylurea, the compounds are outside of the genus in each of the patents-in-suit. The attachment of the 5-position phenyl to a spacer group also puts these compounds outside the genus of the ’823 and ’165 patents, and the genus of claim 1 of the ’068 patent. To the extent Teva argues that the experimental precursors, which are pyrazoles with sulfamyl substituents at the 1-position, each of these compounds has a spacer group between the 5-position of the pyrazole ring and the phenyl and, therefore, is outside the genus of the ’068 patent.

XVI. CELECOXIB IS CLOSER IN STRUCTURE TO SC-58125 THAN TO EXAMPLE 29-3 OF THE ’829 FUJISAWA REFERENCE

156. I understand that Teva argues that Example 29-3 of the ’829 Fujisawa reference is closer in structure to celecoxib than is SC-58125. I disagree. As shown below, SC-58125 and Example 29-3 differ only in the substituent on the phenyl at the 5-position of the pyrazole. Celecoxib has a methyl substituent at that position.

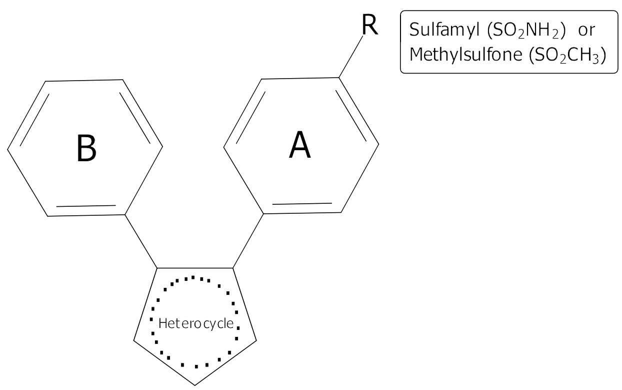
		
Example 29-3	**SC-58125**	**Celecoxib**

132 Soliman *et al*., “Synthesis and Antidiabetic Activity of Some Sulfonylurea Derivatives of 3, 5-Disubstituted Pyrazoles,” Journal of Pharm. Sci., vol. 72, no. 9, pp. 999-1004 (Sept. 1983) (DX-041).

The fluorine (-F) substituent of SC-58125 is closer to the methyl ($-CH_3$) substituent of celecoxib than the nitro ($-NO_2$) substituent of Example 29-3 because: (a) the nitro substituent is viewed as more polar than the fluoro or methyl substituents; (b) the nitro substituent is pi-electron withdrawing on a benzene ring, while fluoro and methyl substituents are pi-electron donating[133]; and (c) the fluoro and methyl groups have similar size (each contains a single non-hydrogen atom), whereas the nitro substituent has three non-hydrogen atoms.[134]

XVII. BASED ON THE REASONING OF TEVA'S EXPERTS, VIOXX® IS AS CLOSE TO CELEBREX® AS ANY OTHER COMPOUND IN THE TEVA PHARMACOPHORE

157. The Teva Pharmacophore contains diphenyl, five-membered heterocycles where one phenyl ring contains a methyl sulfone or sulfamyl substituent, as set forth below:



158. Teva's experts opine that one of ordinary skill in the art would have used the Teva Pharmacophore as the lead rather than using a lead compound,[135] and that all compounds within the Teva Pharmacophore would be expected to be COX-2 selective. This

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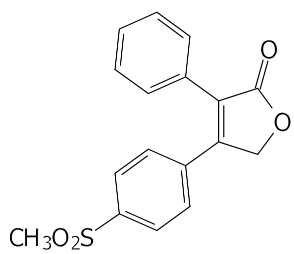
133 This leads to the well-known facts that nitro groups are meta-directing, while fluoro and methyl groups are ortho, para-directing in electrophilic aromatic substitution reactions.

134 Furthermore, based on the reasoning of Teva's experts (not mine), one would not have considered this compound because of the toxicity associated with nitro group. (*See* Trummlitz Rep. ¶87; Baker Rep. ¶163; Cooperman Rep. ¶116).

135 Trummlitz Rep. ¶¶93-98; Baker Rep. ¶¶140-145; Cooperman Rep. ¶¶124-131.

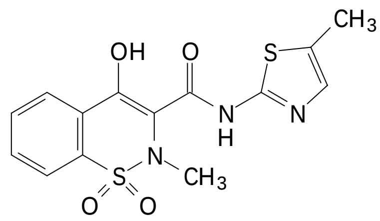
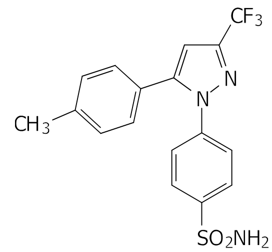
pharmacophore is far too broad to have practical utility as a lead. For example, it is my opinion that Vioxx® (rofecoxib) is structurally distinct from Celebrex® (celecoxib). However, based on the reasoning of Teva's experts (with which I disagree) that: (a) five-membered heterocycles are interchangeable; (b) the sulfamyl and methyl sulfone are interchangeable; (c) the phenyl "B" ring and the heterocycles can be substituted or unsubstituted; and (d) the identities of the "optional" heterocycle and phenyl "B" substituents do not affect COX-2 activity, it is my opinion that Vioxx® (rofecoxib), is as close to celecoxib as any other compound within the Teva Pharmacophore.



Vioxx® (rofecoxib)

XVIII. MELOXICAM DOES NOT TEACH CELECOXIB

159. Dr. Trummlitz says that Boehringer Ingelheim's drug meloxicam "was the first compound launched as a selective COX-2 inhibitor." (Trummlitz Rep. ¶38). To the extent that Dr. Trummlitz cites meloxicam as a COX-2 selective NSAID that predates celecoxib, there is no suggestion in the structure of meloxicam (shown below), which is a not a diphenyl heterocycle, to create celecoxib (also shown below) or any of the compounds within the claimed genus.

	
Meloxicam	**Celecoxib**

Dated: June 23, 2006

Dr. William L. Jorgensen

CERTIFICATE OF SERVICE

I hereby certify that I caused a true and correct copy of the foregoing Expert Report of Dr. William L. Jorgensen to be served by electronic mail on the 23rd day of June 2006 on the counsel for the defendant as follows:

Thomas L. Creel
Keith A. Zullow
GOODWIN PROCTER LLP
599 Lexington Avenue
New York, NY 10022
Fax: 212-355-3333

I hereby certify that I caused a true and correct copy of the foregoing Expert Report of Dr. William L. Jorgensen to be served by first class mail on the 26th day of June 2006 on the counsel for the defendant as follows:

Thomas L. Creel
Keith A. Zullow
GOODWIN PROCTER LLP
599 Lexington Avenue
New York, NY 10022
Fax: 212-355-3333

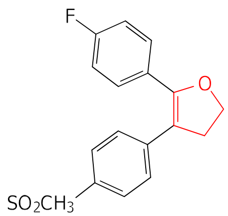
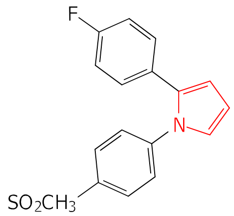
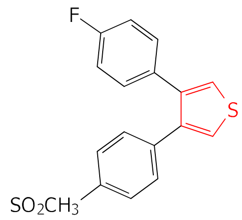
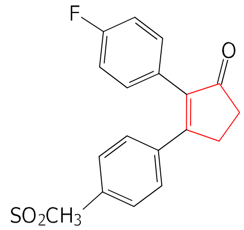
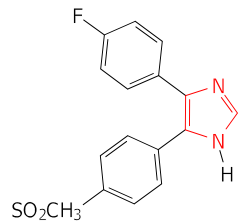
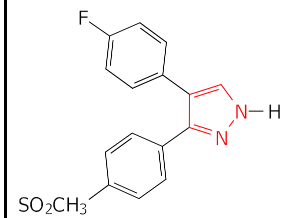
Daniel Reisner

Daniel Reisner

Exhibit 1

EXHIBIT 1

Identity of the Heterocycle

					
SC-58844[136]	**SC-57126**[137]	**MCP-175851**[138]	**SC-58229**[139]	**SC-59873**[140]	**SC58275**[141]
COX-1 IC50: >100μM	COX-1 IC50: >100μM	COX-1 IC50: >100μM	COX-1 IC50: >100μM	COX-1 IC50: >100μM	COX-1 IC50: >100μM
COX-2 IC50: 0.144μM	COX-2 IC50: 0.511μM	COX-2 IC50: 0.0363μM	COX-2 IC50: >100μM	COX-2 IC50: >100μM	COX-2 IC50: >100μM

136 PFC01592163; PFC01571296; PFC01555218.

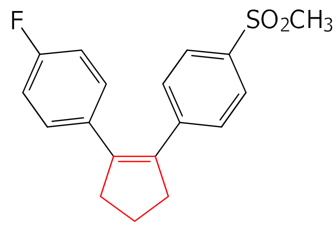
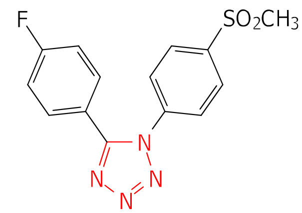
137 PFC01592078; PFC01228762; PFC01554299.

138 PFC01592063.

139 PFC01592124; PFC00306094; PFC01554353.

140 PFC01592236; PFC01575370-71; PFC01556248.

141 PFC01592126; PFC01554460.

	
SC-57666[142]	**SC-57855**[143]
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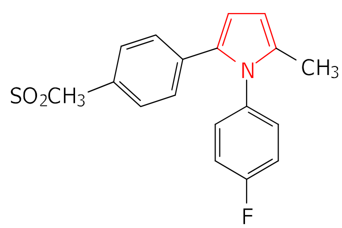
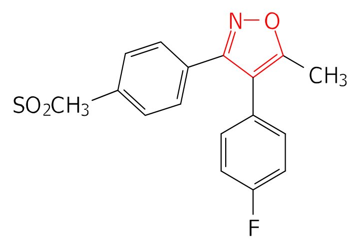
COX-2 IC50: 0.021µM	COX-2 IC50: >100µM

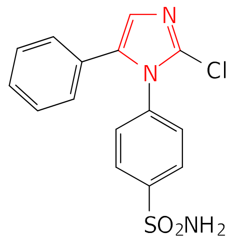
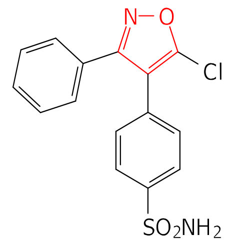
	
SC-57019[144]	**SC-65023**[145]
COX-1 IC50: >100µM	COX-1 IC50: >100µM
COX-2 IC50: 0.0620µM	COX-2 IC50: >100µM

142 PFC01592088; PFC01576133; PFC01554299.

143 PFC01592095; PFC00316100; PFC01554299.

144 PFC01592078; PFC01228796; PFC01552824.

145 PFC01592423; PFC01235130; PFC01558387.

	
SC-67949[146]	**SC-68173**[147]
COX-1 IC50: >100μM	COX-1 IC50: 117μM
COX-2 IC50: >100μM	COX-2 IC50: 0.00672μM

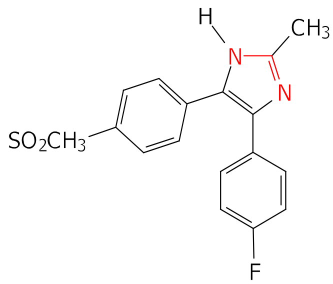
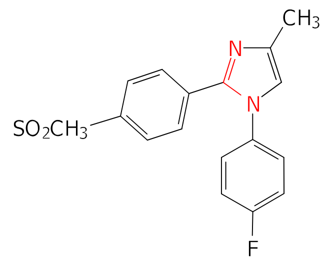
[146] PFC01592515; PFC01559557.

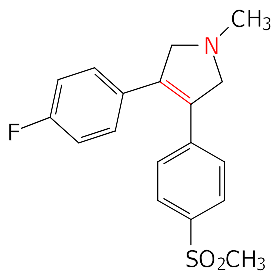
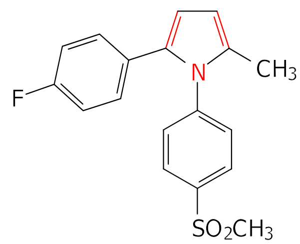
[147] PFC01592520; PFC01231660; PFC01559737.

Exhibit 2

EXHIBIT 2

Position of the Heteroatom

	
SC-59978[148]	**SC-59494**[149]
COX-1 IC50: >100µM	COX-1 IC50: >100µM
COX-2 IC50: 4.24µM	COX-2 IC50: >100µM

	
SC-58308[150]	**SC-56975**[151]
COX-1 IC50: 22.8µM	COX-1 IC50: >100µM
COX-2 IC50: .100µM	COX-2 IC50: >100µM

148 PFC01592240; PFC01575371; PFC01556248.

149 PFC01592210; PFC01230024; PFC01555722.

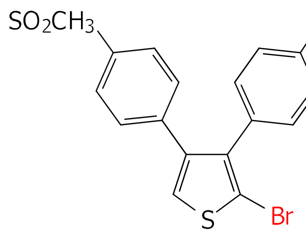
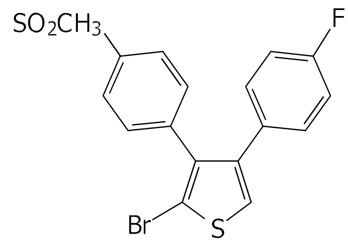
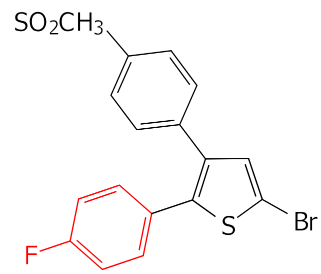
150 PFC01592128; PFC01554488.

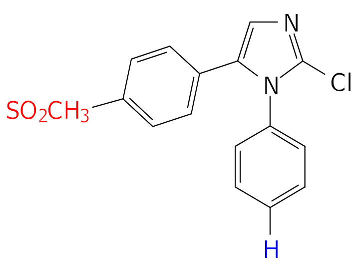
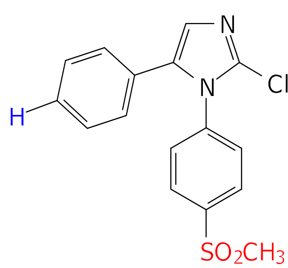
151 PFC01592078; PFC01228721; PFC01552763.

Exhibit 3

EXHIBIT 3

Position of the Phenyl Rings

		
MCP-1785884[152]	**MCP-179015**[153]	**MCP-175722**[154]
COX-1 IC50: >100µM	COX-1 IC50: >100µM	COX-1 IC50: 0.998µM
COX-1 IC50: 5.06µM	COX-2 IC50: >100µM	COX-2 IC50: 0.003µM

	
SC-67779[155]	**SC-67909**[156]
COX-1 IC50: >100µM	COX-1 IC50: >100µM
COX-2 IC50: 0.385µM	COX-2 IC50: >100µM

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152 PFC01592063.

153 PFC01592067; PFC01233290; PFC01552595.

154 PFC01592063; PFC00637981; PFC01554299.

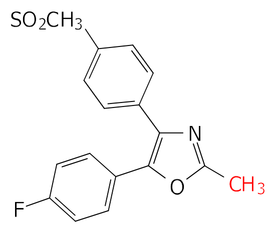
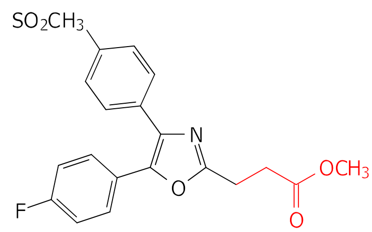
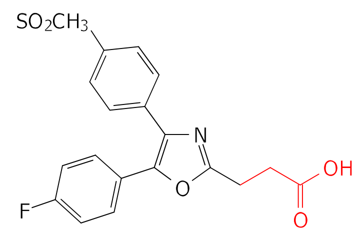
155 PFC01592512.

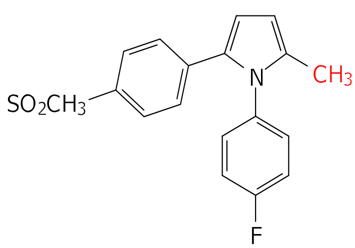
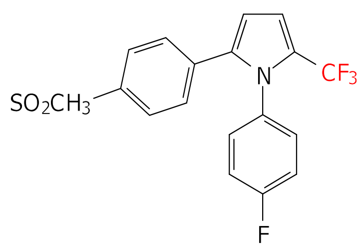
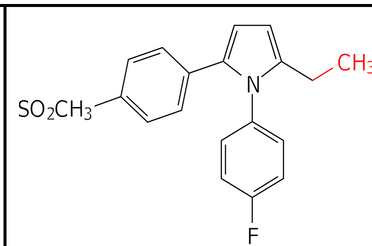
156 PFC01592514; PFC01559557.

Exhibit 4

EXHIBIT 4

Identity, position, and number of the "optional" heterocyle substituent

		
MCP-178944[157]	**MCP-178957**[158]	**MCP-178960**[159]
COX-1 IC50: >30µM	COX-1 IC50: >1000µM	COX-1 IC50: >1000µM
COX-2 IC50: >10µM	COX-2 IC50: 0.249µM	COX-2 IC50: >1000µM

		
SC-57019[160]	**SC-58740**[161]	**SC-58442**[162]
COX-1 IC50: >100µM	COX-1 IC50: >100µM	COX-1 IC50: >100µM
COX-2 IC50: 0.062µM	COX-2 IC50: >100µM	COX-2 IC50: >100µM

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157 PFC01592066; PFC00636851; PFC01553027.

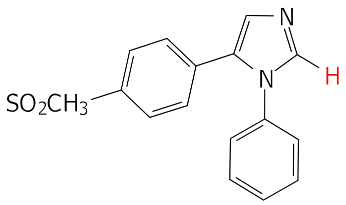
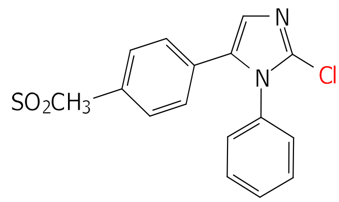
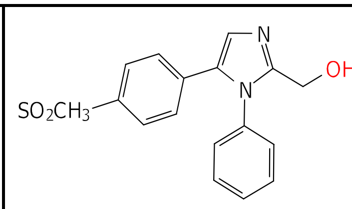
158 PFC01592066; PFC00636844; PFC01553027.

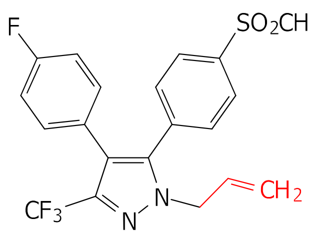
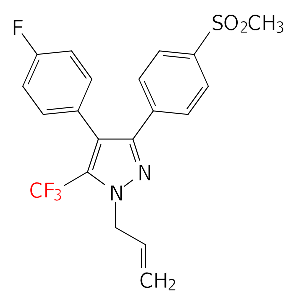
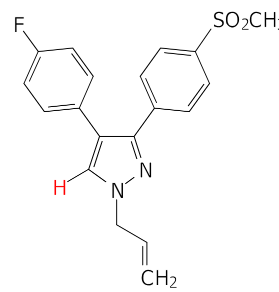
159 PFC01592067; PFC00636846; PFC01205908.

160 PFC01592078; PFC01228796; PFC01552824.

161 PFC01592158; PFC01228879; PFC01554690.

162 PFC01592137; PFC01234136; PFC01554541.

		
SC-67730[163]	**SC-67779[164]**	**X-11173**
COX-1 IC50: >100μM	COX-1 IC50: >100μM	COX-1 IC50: >100μM
COX-2 IC50: >100μM	COX-2 IC50: 0.385μM	COX-2 IC50: >100μM

		
SC-57385[165]	**SC-57384[166]**	**SC-58285[167]**
COX-1 IC50: >500μM	COX-1 IC50: >500μM	COX-1 IC50: >100μM
COX-2 IC50: >500μM	COX-2 IC50: 0.0680μM	COX-2 IC50: >100μM

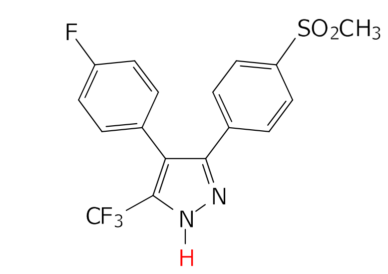
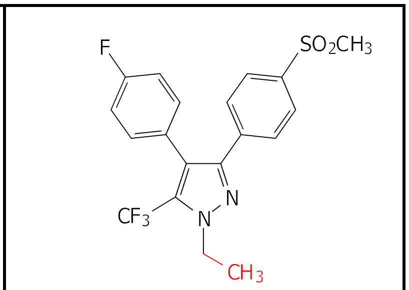
163 PFC01592511; PFC01559334.

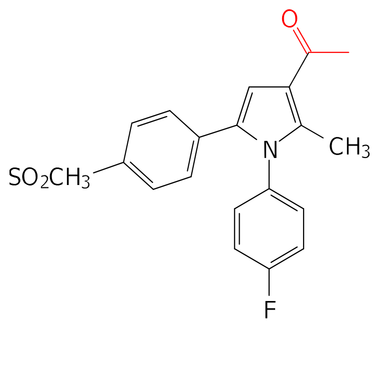
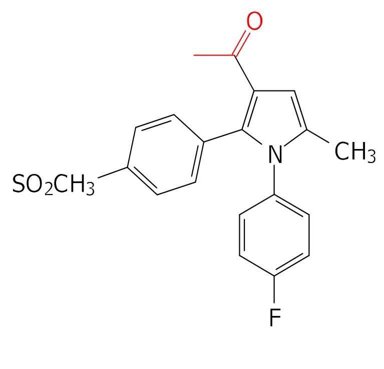
164 PFC01592512.

165 PFC01592082 PFC00637809.

166 PFC01592082; PFC00637809.

167 PFC01592127; PFC01554460.

	
MCP-183583[168]	**MCP-183585**[169]
COX-1:IC50: >100 µM	COX-1:IC50: >100 µM
COX-2:IC50: >100 µM	COX-2:IC50: 0.0965 µM

	
SC-57897[170]	**SC-57898**[171]
COX-1:IC50: >100 µM	COX-1:IC50: >100 µM
COX-2:IC50: 1.58 µM	COX-2:IC50: >100 µM

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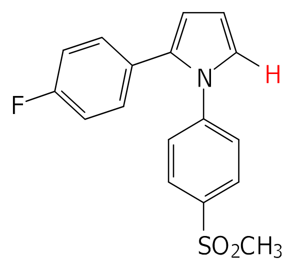
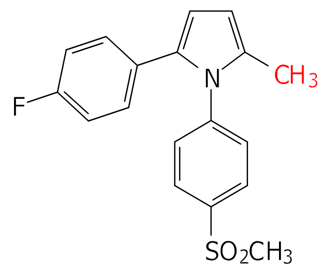
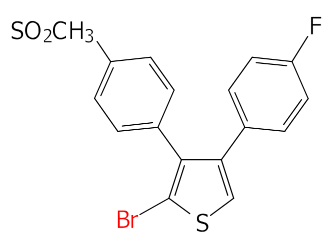
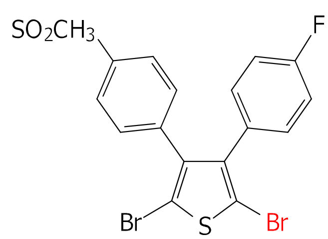
[168] PFC01592075; PFC00637774; PFC01552964.

[169] PFC01592076; PFC00637778; PFC01552964.

[170] PFC01592099; PFC01228801; PFC01554223.

[171] PFC01592099; PFC01228801; PFC01554223.

	
SC-57126[172]	**SC-56975**[173]
COX-1 IC50: >100µM	COX-1 IC50: >100µM
COX-2 IC50: 0.511µM	COX-2 IC50: >100µM

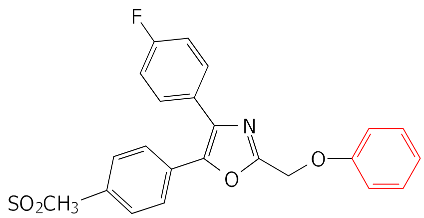
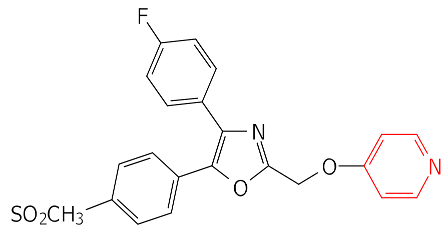
	
MCP-179015[174]	**MCP-178308**[175]
COX-1 IC50: >100µM	COX-1 IC50: >1000µM
COX-2 IC50: >100µM	COX-2 IC50: 0.107µM

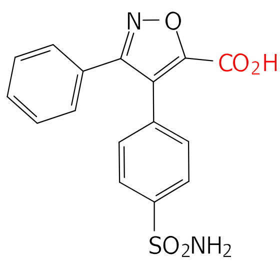
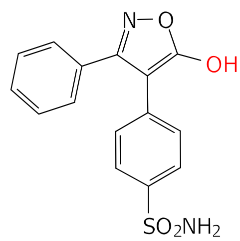
172 PFC01592078; PFC01228762; PFC01554299.

173 PFC01592078; PFC01228721; PFC01552763.

174 PFC01592067; PFC01233290; PFC01552595.

175 PFC01592065; PFC01233248; PFC01552677.

	
SC-58041[176]	**SC-58042**[177]
COX-1 IC50: >100µM	COX-1 IC50: >100µM
COX-2 IC50: 0.0169µM	COX-2 IC50: >100µM

	
SC-67817[178]	**SC-67818**[179]
COX-1 IC50: 1.7µM	COX-1 IC50: >1000µM
COX-2 IC50: 44.8µM	COX-2 IC50: 2.32µM

[176] PFC01592109; PFC00636939; PFC01554299.

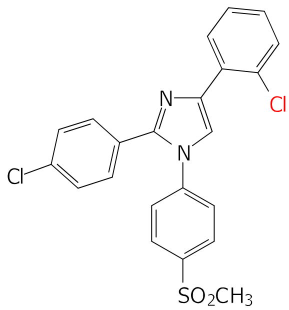
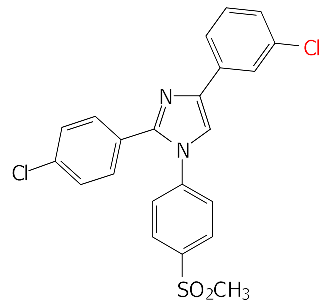
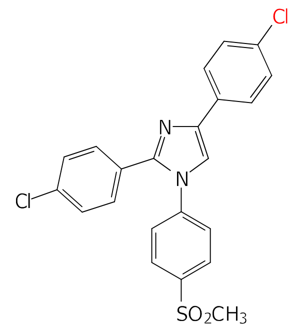
[177] PFC01592109; PFC00636940; PFC01554223.

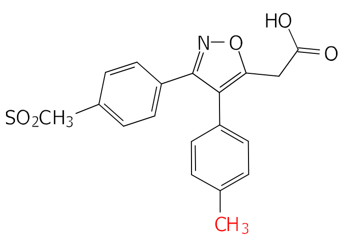
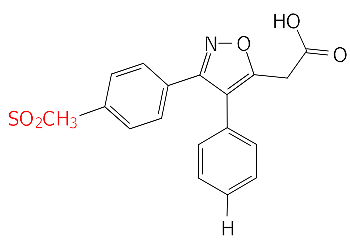
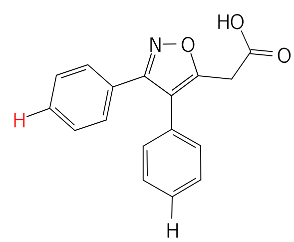
[178] PFC01592512; PFC01231648.

[179] PFC01592513; PFC01231657; PFC01559557.

EXHIBIT 5

Identity, position and number of the "optional" phenyl "B" substituent

		
SC-60753[180]	**SC-60966**[181]	**SC-60937**[182]
COX-1 IC50: >100µM	COX-1 IC50: >100µM	COX-1 IC50: >100µM
COX-2 IC50: >100µM	COX-2 IC50: 0.125µM	COX-2 IC50: 0.451µM

		
SC-65777[183]	**SC-65741**[184]	**SC-65848**[185]
COX-1 IC50: 5.96µM	COX-1 IC50: >100µM	COX-1 IC50: 0.42µM
COX-2 IC50: >100µM	COX-2 IC50: >100µM	COX-2 IC50: 0.014µM

180 PFC01592291; PFC01577142; PFC01556559.

181 PFC01592304; PFC01577153; PFC01556649.

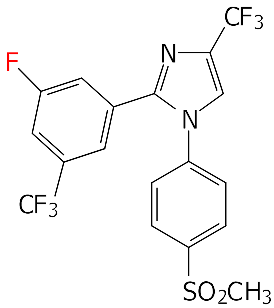
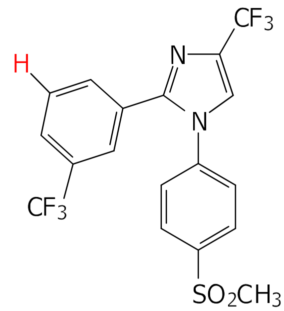
182 PFC01592302; PFC01577156; PFC01556629.

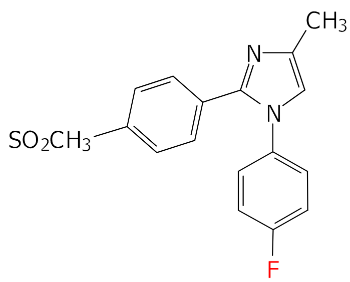
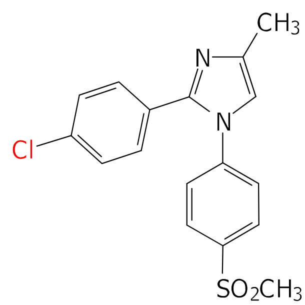
183 PFC01592448; PFC01235162; PFC01558633.

184 PFC01592445; PFC01235159; PFC01558633.

185 PFC01592452; PFC01235169.

Exhibit 5

	
SC-64338[186]	**SC-64539**[187]
COX-1 IC50: 34µM	COX-1 IC50: >100µM
COX-2 IC50: >100µM	COX-2 IC50: 0.370µM

	
SC-59494[188]	**SC-59495**[189]
COX-1 IC50: >100µM	COX-1 IC50: 12.1µM
COX-2 IC50: >100µM	COX-2 IC50: .231µM

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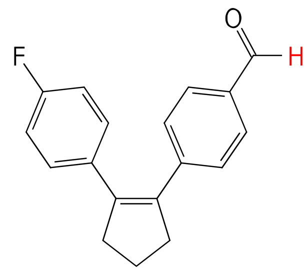
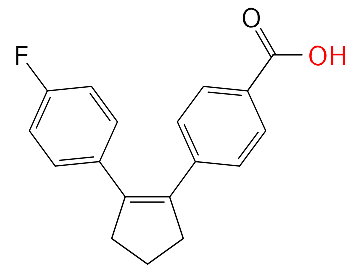
186 PFC01592399; PFC01557624.

187 PFC01592409; PFC01230195; PFC01552546.

188 PFC01592210; PFC01230024; PFC01555722.

189 PFC01592210; PFC01230042; PFC01555746.

	
SC-58898[190]	**SC-58899**[191]
COX-1:IC50: 2.64 µM	COX-1:IC50: >100 µM
COX-2:IC50: >100 µM	COX-2:IC50: >100 µM

[190] PFC01592166; PFC01563963; PFC01555218.

[191] PFC01592166; PFC01563964; PFC01555218.

Exhibit 6

EXHIBIT 6

Compound Number	Reference
MCP-178960	PFC01592067; PFC00636846; PFC01205908
MCP-179015	PFC01592967; PFC01233290; PFC01552595
MCP-179109	PFC01592072; PFC01228721; PFC01552927
MCP-179115	PFC01592074
SC-56975	PFC01592078; PFC01228721; PFC01552763
SC-57484	PFC01592083; PFC01228769; PFC01554299
SC-57604	PFC01592085; PFC01228783; PFC01553874
SC-57605	PFC01592086; PFC01228760; PFC01553874
SC-57853	PFC01592095; PFC00637297; PFC01554113
SC-57854	PFC01592095; PFC00637296; PFC01554113
SC-57877	PFC01592096; PFC00304139; PFC01554192
SC-57896	PFC01592098; PFC01228798; PFC01554223
SC-57898	PFC01592099; PFC01228801; PFC01554223
SC-57931	PFC01592103; PFC01573224; PFC01554192
SC-58042	PFC01592109; PFC00636940; PFC01554223
SC-58056	PFC01592110; PFC01227564; PFC01554223
SC-58088	PFC01592114; PFC00637298; PFC01554299
SC-58093	PFC01592115; PFC01236016; PFC01554299
SC-58104	PFC01592115; PFC00637305; PFC01554299
SC-58144	PFC01592117; PFC00637308; PFC01554299
SC-58159	PFC01592119; PFC01236029-30; PFC01554299
SC-58190	PFC01592121; PFC01236040; PFC01554370
SC-58229	PFC01592124; PFC00306094; PFC01554353
SC-58235	PFC01592125; PFC00637309; PFC01554353
SC-58264	PFC01592126; PFC00304173; PFC01554393
SC-58324	PFC01592129; PFC01554443; PFC01568040
SC-58325	PFC01592130; PFC01554443; PFC01568047

SC-58375	PFC01592131; PFC01234132; PFC01554488
SC-58387	PFC01592133; PFC01226847; PFC01554488
SC-58442	PFC01592137; PFC01234136; PFC01554541
SC-58466	PFC01592138; PFC01234142; PFC01554541
SC-58572	PFC01592146; PFC02229079; PFC01554576
SC-58573	PFC01592146; PFC01229018; PFC01554576
SC-58583	PFC01592147; PFC01234144; PFC01554576
SC-58740	PFC01592158; PFC01228879; PFC01554690
SC-58921	PFC01592168; PFC01577067; PFC01555246
SC-58969	PFC01592173; PFC01576191; PFC01555246
SC-59184	PFC01592185; PFC01229076; PFC01555314
SC-59494	PFC01592210; PFC01230024; PFC01555722
SC-59582	PFC01592212; PFC01555770
SC-59873	PFC01592236; PFC01575370-71; PFC01556248
SC-60245	PFC01592256; PFC01575383; PFC01556399
SC-60302	PFC01592260; PFC01556399
SC-60459	PFC01592273; PFC01575390; PFC01556495
SC-60484	PFC01592275; PFC01575391; PFC01556495
SC-60559	PFC01592278; PFC01575384; PFC01575271; PFC01556495
SC-60561	PFC01592279; PFC01575393; PFC01556495
SC-60608	PFC01592282; PFC01575396; PFC01556511
SC-60621	PFC01592284; PFC01577133; PFC01556511
SC-60660	PFC01592285; PFC01577139; PFC01556511
SC-60701	PFC01592288; PFC01575400; PFC01556539
SC-60753	PFC01592291; PFC01577142; PFC01556559
SC-60755	PFC01592292; PFC01577143; PFC01556559
SC-60791	PFC01592295; PFC01575392; PFC01575271; PFC01556559
SC-60792	PFC01592295; PFC01575392; PFC01575271; PFC01556559
SC-60801	PFC01592296; PFC01577144; PFC01556559

SC-61096	PFC01592310; PFC01556697
SC-62919	PFC01592329; PFC01557111
SC-62920	PFC01592329; PFC01557111
SC-63434	PFC01592355; PFC01557345
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SC-63558	PFC01592365; PFC01557389
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SC-63815	PFC01592378; PFC01557499
SC-64053	PFC01592390; PFC01557551
SC-64273	PFC01592397; PFC01557613
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SC-64338	PFC01592399; PFC01557624
SC-64514	PFC01592408; PFC01202523
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SC-65045	PFC01592423; PFC01235134; PFC01558409
SC-65083	PFC01592426; PFC01558423
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SC-65614	PFC01592438; PFC01235152; PFC01558529
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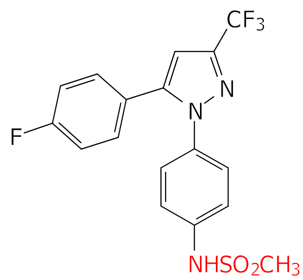
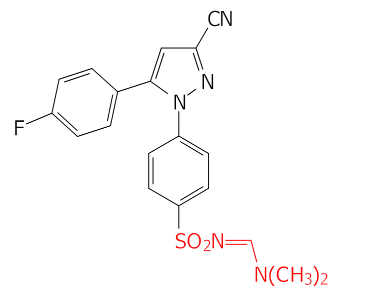
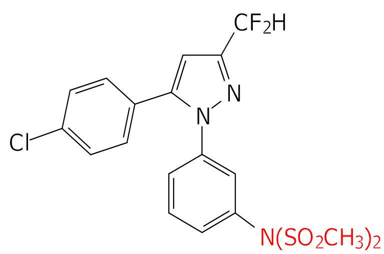
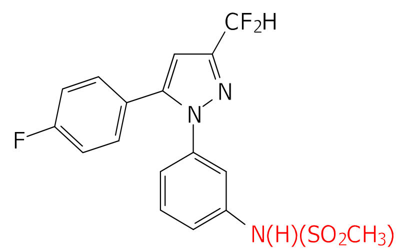
SC-65747	PFC01592446; PFC01558667
SC-65767	PFC01592447; PFC01230765; PFC01558689
SC-65777	PFC01592448; PFC01235162; PFC01558633

SC-65828	PFC01592452; PFC01558689
SC-66071	PFC01592459; PFC01231299; PFC01558751
SC-66088	PFC01592460; PFC01558811
SC-66676	PFC01592487; PFC01231143; PFC01559038
SC-66678	PFC01592487; PFC01231142; PFC01559038
SC-66967	PFC01592498; PFC00637152; PFC01559136
SC-67274	PFC01592503
SC-67442	PFC01592506; PFC01559262
SC-67443	PFC01592507; PFC01559262
SC-67561	PFC01592508; PFC01231726; PFC01559287
SC-67730	PFC01592511; PFC01559334
SC-67909	PFC01592514; PFC01559557
SC-67949	PFC01592515; PFC01559557
SC-68026	PFC01592516; PFC01559567
X-11173	PFC01592523; PFC01559557

Exhibit 7

EXHIBIT 7

Sulfonamide Analogs

	
SC-58928[192]	**SC-58985**[193]
COX-1:IC50: >100 μM	COX-1:IC50: >100 μM
COX-2:IC50: >100 μM	COX-2:IC50: >100 μM
	
SC-59078[194]	**SC-59296**[195]
COX-1:IC50: >100 μM	COX-1:IC50: >100 μM
COX-2:IC50: >100 μM	COX-2:IC50: >100 μM

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192 PFC01592169; PFC00657096; PFC01555218.

193 PFC01592174.

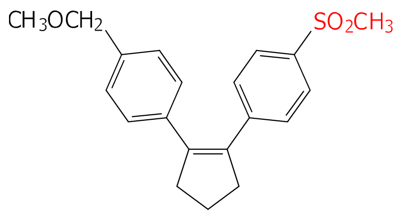
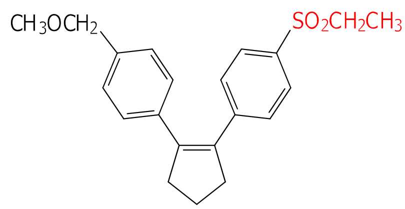
194 PFC01592180; PFC00657096; PFC01555218.

195 PFC01592193.

Exhibit 8

EXHIBIT 8

Sulfone Analogs

	
SC-58263[196]	**SC-58262**[197]
COX-1:IC50: >100 µM	COX-1:IC50: >100 µM
COX-2:IC50: 6µM	COX-2:IC50: >100µM

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196 PFC01592126; PFC00304172; PFC01554408.

197 PFC01592126; PFC00304172; PFC01554408.

Exhibit A

06/06

VITA OF WILLIAM L. JORGENSEN

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Telephone:	(203) 432-6278

Date of Birth:	October 5, 1949
Place of Birth:	New York, New York

Education

A.B. in Chemistry, 1970:	Princeton University, Princeton, New Jersey
Ph.D. in Chemical Physics, 1975:	Harvard University, Cambridge, Massachusetts

Employment

1968-1970	Research Assistant, Princeton University. Computational methods in molecular quantum mechanics (L. C. Allen).
1970-1975	Graduate student and briefly postdoctoral fellow, Harvard University. Computer assisted synthetic analysis (E. J. Corey) and theoretical chemistry (W. Borden, L. Salem).
1975-1979	Assistant Professor, Department of Chemistry, Purdue University.
1979-1982	Associate Professor, Department of Chemistry, Purdue University.
1982-1990	Professor, Department of Chemistry, Purdue University.
1984-1987	Head, Organic Chemistry Division, Purdue University.
1985-1990	Herbert C. Brown Professor of Chemistry, Purdue University.
1989	Visiting Professor, Harvard University.
1990-	Whitehead Professor of Chemistry, Yale University.

Honors

2004 Sato Memorial International Award - Pharmaceutical Society of Japan
2004 Award in Computational Biology – Intl. Society for Quantum Biology & Pharmacology
1998 Award for Computers in Chemical and Pharmaceutical Research – Amer. Chemical Soc.
1994 Fellow, American Association for the Advancement of Science
1990 Arthur C. Cope Scholar Award, American Chemical Society
Special Creativity Award, National Science Foundation, 1990-1992
Special Creativity Award, National Science Foundation, 1989-1991
1986 Annual Medal of the International Academy of Quantum Molecular Sciences
Camille and Henry Dreyfus Foundation Teacher-Scholar, 1978-1983
Alfred P. Sloan Foundation Fellow, 1979-1981
A.B. summa cum laude; McCay Prize (undergraduate)

Editor

Encyclopedia of Computational Chemistry, 2001-2005
Journal of Computational Chemistry, 2002 –2003
Journal of Chemical Information and Computer Sciences (JCICS), 2004
Journal of Chemical Information and Modeling (formerly JCICS), 2005-
Journal of Chemical Theory and Computation, 2005-

Member or Officer

National Institutes of Health, Medicinal Chemistry A Study Section, 2001-2004
American Chemical Society -
    Chairman-Elect, Computers in Chemistry Division, 2001; Chairman, 2002
International Society for Quantum Biology and Pharmacology -
    Vice President, 2000; President, 2001-2002

Memberships on Advisory Boards

Analyst for Data Trace, Inc. (Chemtracts) 1986-98
Advisory Committee, NIH Regional NMR Center, 1986-90
Scientific Advisory Board, Evans & Sutherland Inc., 1987-92
Scientific Advisory Board, Ariad Pharmaceuticals Inc., 1991-
Scientific Advisory Board, CombiChem Inc., 1994-1999
Scientific Advisory Board, Schrödinger Inc., 1996-
Scientific Advisory Board & Founder, Rib-X Pharmaceutical Inc., 2001-
Current Consultant: Pfizer Global Research
Past Consultant: Agouron Pharmaceuticals, Parke-Davis, Pharmacia
W. Gibbs Medal Nominating Committee, 2001-2004
AAAS Electorate Nominating Committee, 2003-2006; Chair, 2004
World Association of Theoretical & Computational Chemists (WATOC), 2003-
ACS Executive Director's Committee, 2004-
ACS Assessing the IT Future Committee, 2006
J. Allyn Taylor International Prize in Medicine Committee, 2006

Editorial Advisory Boards:
Journal of the American Chemical Society, 1987-93
CRC Critical Reviews in Theoretical Chemistry and Biophysics, 1987-93
Journal of Physical Organic Chemistry, 1987-94
Journal of Computational Chemistry, 1989-2003
Theoretica Chimica Acta, 1990-94
Theoretical Chemistry Accounts, 1997-2002
Bioorganic and Medicinal Chemistry Letters, 1990-
Bioorganic and Medicinal Chemistry, 1992-
Journal of Computer Aided Molecular Design, 1992-
Supramolecular Chemistry, 1992-
Chemistry and Biology, 1994-2004
Accounts of Chemical Research, 2001-2004

Memberships in Professional Societies

American Chemical Society
American Association for the Advancement of Science
International Society for Quantum Biology and Pharmacology
International AIDS Society
World Association of Theoretical & Computational Chemists
Connecticut Academy of Arts and Sciences

Publications - W. L. Jorgensen

1. Structural and Energetic Predictions for Simple Hydrocarbons from the NDDO and CNDO Semiempirical Molecular OrbitalMethods.
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   J. Am. Chem. Soc., 93, 567 (1971).

4. Chemical Consequences of Orbital Interactions in Hydrocarbons Containing Unsaturatively Bridged Small Rings.
   W. L. Jorgensen and W. T. Borden
   J. Am. Chem. Soc., 95, 6649 (1973).

5. "The Organic Chemist's Book of Orbitals".
   W. L. Jorgensen and L. Salem
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   In German, "Orbitale Organischer Molekule", Verlag Chemie. Weinheim/Bergstr., 1974.

6. Orbital Interactions in Molecules Containing Unsaturatively Bridged Cyclobutane and Bicyclobutane Rings.
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   J. Am. Chem. Soc., 98, 189 (1976).

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    J. Am. Chem. Soc., 98, 6784 (1976).

11. The Behavior of Trishomocyclopropenyl Cations.
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    Tetrahedron Letters, 3027 (1976).

12. The Structure and Stability of Coates' Cations.
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13. The Cyclic Structure of Monomeric Dilithioacetylene.
    Y. Apeloig, P. v. R. Schleyer, J. S. Binkley, J. A. Pople, and W. L. Jorgensen
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    W. L. Jorgensen
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    J. Am. Chem. Soc., 99, 4272 (1977).

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    J. Am. Chem. Soc., 99, 3840 (1977).

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W. L. Jorgensen
J. Phys. Chem., 87, 5304 (1983).

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Y. Munoz-Sola, R. Strommen, and B. Pandey
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Invited Lectures

Dr. Jorgensen has presented more than 500 invited lectures including such distinguished lectureships as 7th Marvel Symposium, 15th Leermakers Symposium, 1988 Nobel Symposium, Organic Synthesis Distinguished Lecturer, Syntex Syposium (U. Colorado), 6th W. S. Johnson Lectures, Steiglitz Memorial Lecturer, Drew U. Research Scholar Lecturer, Royal Society Faraday and Perkin Lectures, Visiting Lecturer - ETH Zürich, 34th National Organic Symposium, Tetrahedron Symposium, Tanabe Lecturer - Scripps, Hirschmann Lecturer - Oberlin, Gunning Lecturer - University of Alberta, H. C. Brown Lecturer – Purdue, Schleyer Lecturer - U. Georgia, ISQBP Plenary Lecturer, BMS Lecturer - Scripps, 3eme Cycle Lecturer – Switzerland.

Recent Invited Lectures (1998-)

1998

Faraday Discussion on Chemical Reaction Theory - St. Andrews, Scotland
15th H. C. Brown Lectures - Purdue University
NATO ARW on Supramolecular Science - Lerici, Italy
Novartis Workshop on Structure-Based Drug Design - Summit, NJ
National ACS Meeting - Computers in Chem. & Pharm. Research Award - Dallas
National ACS Meeting - Symposium on Transition State Modeling - Dallas
Frederick Cancer R & D Center – Frederick, MD
University of Maryland
Glaxo-Wellcome, RTP, NC
Wyeth-Ayerst, Princeton
Agouron Pharmaceuticals - La Jolla, CA
Chemistry & Biology Symposium - Yale University
Parke-Davis Pharmaceutical Co. - Ann Arbor, MI
National ACS Meeting - Symposium on Polymers in Aq. Media - Boston
National ACS Meeting - Symposium on Force Fields - Boston
Yale Cancer Center
Wesleyan University

1999

11th Argentinian Conference on Physical Organic Chemistry - Sante Fe
WATOC-99 – London
National ACS Meeting - Symposium on Water in Chemistry & Biology - New Orleans
National ACS Meeting - Symposium on Docking & Scoring - New Orleans
University of Georgia
Schrödinger Inc.
UC San Francisco - DOCK User's Group Meeting
CombiChem Inc.
Vertex Pharmaceuticals Inc.
Gordon Conference on QSAR
Western Maryland College – Building Dedication

Pharmacopeia Inc.
8th Conf. on Trends in Computational Chemistry, Vicksburg, MS
Parke-Davis Pharmaceuticals
Pharmacia and Upjohn, Inc.

2000
National ACS Meeting - Symposium on Potential Energy Surfaces - San Francisco
National ACS Meeting – Computational Chemistry Award Symposium - San Francisco
National ACS Meeting – Symposium on Drug Design - San Francisco
Computational Chemistry Symposium Honoring P. Schleyer – Hong Kong
Computational Biophysics 2000 – Nice, France
Sanibel Conference – St. Augustine
Texas Christian University
Southern Methodist University
University of Pennsylvania
Beilstein Workshop on Chemical Data Analysis (Bozon)
CECAM Meeting on Challenges for Free Energy Calculations (Lyon)
National ACS Meeting – Frontiers in Biophysical Theory Symposium – Washington DC
IBM – Blue Gene Group – Yorktown Heights
Columbia University
Pharmacia/Upjohn – Kalamazoo
Pharmacia/Searle – Skokie, IL
Pharmacia/Monsanto – St. Louis
Gordon Conference on Computational Chemistry (Oxford)
ACS Short Course on Frontiers in Organic Chemistry, Washington DC

2001
Computational Structural Biology Symposium – Florida State U.
Retrometabolism Drug Design Conference – Amelia Is.
Gordon Conference on Physical Organic Chemistry (Holderness)
Gordon Conference on Biological Molecules in the Gas Phase (CT College)
Molecular Quantum Mechanics Conference Honoring E. Davidson – Seattle
International Conference on Cancer Research (Albany)
10th Conf. on Trends in Computational Chemistry, Jackson, MS
New York University
National ACS Meeting – Libraries for Drug Discovery Symposium - San Diego
Nemethy Symposium, Mt. Sinai School of Medicine
Schrödinger, Inc., New York
Int'l Meeting of the Molecular Graphics & Modeling Society – Erlangen (cancelled, 9/11)
NCI Fluid Properties Symposium
Annual Meeting -Society for Biomolecular Screening, ADME Symposium, Baltimore
Cornell Theory Center Symposium on Protein Structure Prediction
Workshop on Polarizability for Biomolecular Simulations, Snowbird, Utah

2002

Aventis Pharmaceuticals, Bridgewater, NJ
Mesilla Conference on Asymmetric Catalysis
Biophysical Society – Symposium on Molecular Simulations in Biology – San Francisco
National ACS Meeting – Symposium on Drug Design - Orlando
National ACS Meeting – Kollman Memorial Symposium - Orlando
Beilstein Workshop on Molecular Informatics
ISQBP President's Meeting – organizer
ACS Short Course - Philadelphia
WATOC Meeting – Lugano
SPECS Conference on New Chemistries, Delft
Volkswagen Symposium, Ulm
Gordon Conference on Computational Chemistry
University of Delaware

2003

National ACS Meeting – Comp. Chem. Award Symposium for K. N. Houk
Sigma Xi - Connecticut
Cambridge Healthtech Symposium on Drug Design – Philadelphia
AstraZeneca – Wilmington, DE
Locus Development - Philadelphia
Duquesne University
CT Quantum Chemistry Group
Schleyer Lecturer – Univ. of Georgia
UCLA
ACS Short Course – Boston
Celera Genomics
National ACS Meeting, NYC – Symposium on Drug Design
aaiPharma – Wilmington, NC
Schering-Plough – Kenilworth, NJ
DuPont – Newark, DE
US, Polish, Czech Workshop on Biomolecular Interactions - Prague

2004

National ACS Meeting – Symposium on Drug Design - Anaheim
National ACS Meeting – 1st Dewar Symposium – Anaheim
National ACS Meeting – COMP Award Symposium for G. Richards
Bristol-Myers Squibb Lecturer - Scripps Research Institute
ISQBP President's Meeting, Plenary – Como, Italy
Symposium on Computational Chemical Dynamics – U. Minn.
Computational Chemistry Symposium, Plenary – Gyeongju, Korea
3eme Cycle Lecturer – Switzerland :

    University of Basel (3 lectures)
    University of Bern

University of Lausanne
Tetrahedron Symposium on Chemistry and Drug Discovery, New York City
Neurocrine Biosciences – San Diego, CA
Hoffmann La Roche – Nutley, NJ
Rutgers University
Merck – West Point, PA
Yale - Parallel Computing Workshop
D. E. Shaw & Co.
National ACS Meeting- Phila. – Protein Docking & Scoring Symposium
National ACS Meeting- Phila. – Skolnik Award Symposium for A. P. Johnson
MGMS Symposium on Biomolecular Recognition and Reactivity - Manchester UK
University of Arizona – Pharmacology
University of Pennsylvania – Symposium on Structure-Based Drug Design
Schrodinger Users Group – Boston
University of New Haven – Medicinal Chemistry Symposium
Johnson & Johnson – Spring House, PA
Yale - Center for Structural Biology
Soc. Royale de Chimie Belge – Medicinal Chemistry Symposium, Ghent
Wyeth-Ayerst - Cambridge

2005
WATOC Conference – Cape Town
University of Tennessee
Penn State University
Pharmaceutical Society of Japan - Tokyo - Sato Award Presentation
National ACS Meeting- San Diego – J. A. Pople Memorial Symposium
National ACS Meeting- San Diego – Drug Design Symposium
Novartis (Cambridge)
Structural Biology Sympoium - UT Medical Branch (Galveston, TX)
International AIDS Society (Rio)
Univ. Federal do Rio de Janeiro
NIH Docking Workshop
Pfizer (Groton)
ACS Prospectives Symposium on Drug Design
Pacifichem 2005 – Honolulu - Classical and QSM Solvation Symposium
Pacifichem 2005 – Honolulu - Structure, Dynamics, Function of Biomolecules Symposium

2006

Molecular Graphics & Modeling Society (Southampton, UK)
XIIth International Congress of Quantum Chemistry (Kyoto)
Biomolecular Simulation Symposium (Heraeus Found., Bad Honnef)
Texas A&M - IUCCP Pharma Symposium
Johnson & Johnson – La Jolla, CA
National ACS Meeting- Atlanta - Virtual Screening Symposium
PharmaDiscovery 2006 (Bethesda, MD)
CHI Symposium on Structure-Based Drug Design (Boston)
Ohio State University
University of Michigan
City College of New York
Schrodinger Global Users Group Meting (New York City)
Pfizer - Ann Arbor
Boehringer-Ingelheim (Ridgefield)
Oxford University (UK) - G. Richards Symposium
Medicinal Chemistry Symposium (Swedish Chemical Society) - Umeå, Sweden

2007

Pulay Conference - Budapest
European Symposium on Organic Reactivity - Faro, Portugal
AACR/ACS Symposium - Chemistry in Cancer Research (San Diego)
National ACS Meeting- Chicago - Rational Drug Design Symposium
Sanibel Conference

Research Support

Dr. Jorgensen has had uninterrupted research support from the National Science Foundation since 1977 and from the National Institutes of Health since 1980. He currently has research grants from the NSF, the National Institute of General Medical Sciences, the National Institute of Allergy and Infectious Diseases, National Foundation for Cancer Research, and DARPA. Dr. Jorgensen is also part of the Biophysical Training Grant at Yale. Postdoctoral fellows in his laboratory are often supported by national and industrial fellowships - recently, NIH, EMBO, Roche Research Foundation, Bayer Pharmaceuticals, and the governments of Spain and Brazil. A NATO travel grant was shared by Dr. Jorgensen and Dr. F. van Veggel at the University of Twente.

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Prof. Richard Smith (V. P., 1999-)
Dr. Marilyn Kroeger-Smith (1999-)
Ivan Tubert-Brohman (Ph.D., 2006)
Theresa Lyons (Ph.D., 2007)
Siegfried Leund (Ph. D., 2008)
Sara Nichols (Ph.D., 2008)
Laura Thomas (Ph.D., 2009)
Dr. Patrick S. Lee (P.D., 2003-)
Dr. Orlando Acevedo (P.D., 2003-)
Dr. Kurt Sattelmeyer (P.D., 2004-)
Dr. Kasper Jensen (P.D., 2005-)
Dr. Anastassia Alexandrova (P.D., 2005-)
Dr. Joseph Kim (P.D., 2005-)
Dr. Vinay Thakhur (P.D., 2005-)

Past Co-workers

John E. Munroe (M. S., 1977)
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Dr. Pascal Metivier (P.D., 1985-6)
Mark Bures (Ph.D., 1987)
Alan Gushurst (Ph.D., 1988)
Stephane Boudon (1987-9)
Kathleen A. Novak (M.S., 1989)
Weiya Yun (M.S., 1990)
Scott G. Wierschke (M.S., 1990)
Dr. Julianto Pranata (P.D., 1988-91)
Dr. Scott A. Gothe (P.D., 1989-92)
Harold Helson (Ph.D., l993)
Toan Nguyen (Ph.D., 1993)
Jan M. Fleischer (Ph.D., 1994)
Daniel L. Severance (Ph.D., 1993)
David Maxwell (Ph.D., 1995)
Ingvar Lagerstedt (P.D., 1992-4)
Dr. Arshad Khan (Visiting Prof., 1996)
Vickie Tsu (B.S., 1997)
Rong Liu (Ph.D., 1996)
Dr. Deborah Jones-Hertzog (P.D., 1994-6)
Dr. Wolfgang Damm (P.D., 1995-7)
Michelle Lamb (Ph.D., 1997)
Iordanis Houdaverdis (Ph.D., 1998)
Dr. Dongchul Lim (P.D., 1996-98)
Dr. Willem P. van Hoorn (P.D., 1997-99)
Albert C. Pierce (Ph. D., 2000)
Dr. DePing Wang (P.D., 1999-2001)

Jiali Gao (Ph.D., 1987)
Dr. Mustafa Ibrahim (Vis. Prof., 1987-8)
Cynthia MacMahon (M.S., 1989)
J. Kathleen Buckner (Ph.D., 1988)
Ralph T. Mosley (M.S., 1989)
James Briggs (Ph.D., 1990)
Dr. James F. Blake (Ph.D., 1990; P.D., 90-91)
Tooru Matsui (P.D., 1989-91)
Dr. Genevieve Paderes (Ph.D., 1988; P.D., 88-91)
Dr. Ellen R. Laird (Ph.D., 1990; P.D., 90-92)
Prof. Modesto Orozco (V.P., 1991-93)
Shenna Sinclair (Ph.D., 1994)
Erin M. Duffy (Ph.D., 1994)
Jonathan Essex (P.D., 1992-4)
Daqing Gao (M. S., 1995)
Heather Carlson (Ph.D., 1996)
Wendy Schaeffer (B.S., 1997)
Dr. Antonio Frontera (P.D., 1995-6)
George Kaminski (Ph.D., 1997)
Nora McDonald (Ph.D., 1998)
Corky Jenson (M.S.., 1999)
Melissa Plount (Ph.D., 2000)
Daniel Price (Ph.D., 2000)
Michael Mahoney (Ph.D., 2000)
Shane Shariffskul (B.S., 2001)
Dr. Steven S. Wesolowski (P.D., 2000-3)

Dr. Edward Watkins (Assoc. Res. Scientist, 1999-2001)

Robert C. Rizzo (Ph.D., 2000)
Dennis Ostrovsky (Ph.D., 2003)
Dr. Yukio Tominaga (P.D., 2001-3)
Jakob Ulmschneider (Ph.D., 2004)
Dr. Cristiano Guimaraes (P.D., 2001-5)
Dr. Gabriela Barriero (P.D., 2004-5)

Matthew P. Repasky (Ph.D., 2001)
Shoshannah Pearlman (M.S.,2001)
Marina Udier-Blagovic (Ph.D., 2004)
Dr. Juliana Ruiz-Caro (P.D., 2004-5)

Exhibit B

Exhibit B
Documents Reviewed

Production Documents:

PFC00198834 - PFC00198840	PFC00238777 - PFC00238781	PFC00270564 - PFC00270571
PFC00288702 - PFC00288800	PFC00290243 - PFC00290279	PFC00291097 - PFC00291132
PFC00303984 - PFC00304198	PFC00305952 - PFC00306167	PFC00636900 - PFC00636960
PFC00637069 - PFC00637230	PFC00650443 - PFC00650474	PFC00655886 - PFC00655907
PFC00668843 - PFC00668877	PFC00670295 - PFC00670296	PFC01226795 - PFC01226867
PFC01227415 - PFC01227624	PFC01228292 - PFC01228501	PFC01228982 - PFC01229162
PFC01230011 - PFC01230223	PFC01230638 - PFC01230843	PFC01235082 - PFC01235285
PFC01499618 - PFC01499624	PFC01499637 - PFC01499647	PFC01499771 - PFC01499791
PFC01548171 - PFC01548319	PFC01552538 - PFC01552641	PFC01552746 - PFC01552849
PFC01552850 - PFC01552954	PFC01552955 - PFC01553058	PFC01553824 - PFC01553930
PFC01554035 - PFC01554138	PFC01554165 - PFC01554268	PFC01554269 - PFC01554374
PFC01554269 - PFC01554374	PFC01554375 - PFC01554480	PFC01554904 - PFC01555110
PFC01555519 - PFC01555722	PFC01555723 - PFC01555926	PFC01556367 - PFC01556571
PFC01556572 - PFC01556775	PFC01557023 - PFC01557227	PFC01557228 - PFC01557431
PFC01557432 - PFC01557635	PFC01558352 - PFC01558557	PFC01558558 - PFC01558763
PFC01558786 - PFC01558993	PFC01558994 - PFC01559200	PFC01559201 - PFC01559339
PFC01559544 - PFC01559751	PFC01561149 - PFC01561150	PFC01573045 - PFC01573259
PFC01575268 - PFC01575472	PFC01576104 - PFC01576316	PFC01577040 - PFC01577246
PFC01578962 - PFC01578972	PFC01591975 - PFC01591990	PFC01592062 - PFC01593450
PFC01597359 - PFC01597456	PFC01602500 - PFC01602503	PFC01602504 - PFC01602516
PFC01602524 - PFC01602534	PFC01602680 - PFC01602688	PFC01602707 - PFC01602717
PFC01602718 - PFC01602726	PFC01602727 - PFC01602746	PFC01602750 - PFC01602800
PFC01602814 - PFC01602818	PFC01602819 - PFC01602828	PFC01602829 - PFC01602833
PFC01602834 - PFC01602841	PFC01602842 - PFC01602879	PFC01602961 - PFC01602963
PFC01602964 - PFC01602976	PFC01602977 - PFC01602985	PFC01602986 - PFC01602996
PFC01602997 - PFC01603001	PFC01603002 - PFC01603072	PFC01603073 - PFC01603076
PFC01603077 - PFC01603082	PFC01603083 - PFC01603084	PFC01603117 - PFC01603184
PFC01603225 - PFC01603229	PFC01603239 - PFC01603246	PFC01603247 - PFC01603255
PFC01603261 - PFC01603267	PFC01603277 - PFC01603284	PFC01603406 - PFC01603415
PFC01603485 - PFC01603491	PFC01603492 - PFC01603494	PFC01603511 - PFC01603517
PFC01603518 - PFC01603522	PFC01603523 - PFC01603527	PFC01603528 - PFC01603533
PFC01603534 - PFC01603538	PFC01603547 - PFC01603580	PFC01603582 - PFC01603659
PFC01603667 - PFC01603671	PFC01603672 - PFC01603675	PFC01603676 - PFC01603680
PFC01604040 - PFC01604048	PFC01604055 - PFC01604075	PFC01604076 - PFC01604083
PFC01604084 - PFC01604099	PFC01604108 - PFC01604115	PFC01604116 - PFC01604120
PFC01604130 - PFC01604138	PFC01604183 - PFC01604187	PFC01604219 - PFC01604257
PFC01604304 - PFC01604314	PFC01604322 - PFC01604325	PFC01604326 - PFC01604329
PFC01604330 - PFC01604341	PFC01604397 - PFC01604437	PFC01605061 - PFC01605065
PFC01605092 - PFC01605095	PFC01605120 - PFC01605129	PFC01605130 - PFC01605137
PFC01605619 - PFC01605629	PFC01605630 - PFC01605638	PFC01605639 - PFC01605649
PFC01605696 - PFC01605700	PFC01606288 - PFC01606315	PFC01606363 - PFC01606377

PFC01606414 - PFC01606443	PFC01606456 - PFC01606460	PFC01606461 - PFC01606478

Deposition Exhibits:

DX 003	DX 008	DX 012
DX 012A	DX 026	DX 029
DX 033	DX 037	DX 038
DX 040	DX 041	DX 042
DX 043	DX 046	DX 049
DX 051	DX 052	DX 063
DX 068	DX 123	DX 125
DX 138	DX 146	DX 150
DX 151	DX 152	DX 160
DX 186	DX 187	DX 201
DX 202	DX 203	DX 204
DX 205	DX 209	DX 211
DX 234A	DX 241	DX 244
DX 255	PX 031	PX 047

Deposition Transcripts:

Bulock	1/27/2006
Bulock	2/15/2006
Carter	11/8/2005
Collins	12/7/2005
Docter	10/6/2005
Graneto	11/10/2005
Khanna	11/30/2005
Koboldt	1/13/2006
Miyashiro	11/3/2005
Penning	11/4/2005
Talley	1/24/2006
Talley	1/25/2006

Expert Reports:

Baker	5/5/2006
Cooperman	5/5/2006
Galbraith	5/5/2006
Galbraith	6/23/2006
Seibert	6/23/2006
Tummlitz	5/5/2006

Case Documents:

Pfizer's Responses to Defendant Teva Pharmaceutical USA, Inc.'s Third Set of Requests for Admissions	2/9/2006

Other:

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U.S. Patent 4,870,107
U.S. Patent 4,929,643
U.S. Patent 5,143,937
U.S. Patent 5,276,179
U.S. Patent 5,281,626